DISSERTATION ON
"DIAGNOSTIC APPROACH AND MANAGEMENT STRATEGIES OF INVASIVE FUNGAL SINUSITIS"

Dissertation submitted in partial fulfillment of the regulations for the award of the

DEGREE OF M.S.DEGREE BRANCH-IV OTORHINOLARYNGOLOGY

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UPGRADED INSTITUTE OF OTORHINOLARYNGOLOGY, MADRAS MEDICAL COLLEGE, CHENNAI.

APRIL 2017

CERTIFICATE

This is to certify that this dissertation **"A Study On Diagnostic Approach and management strategies of Invasive fungal sinusitis "** submitted by **Dr.S.SUJAYKUMAR,** appearing for M.S ENT Branch IV Degree examination in April 2017 is a bonafide record of work done by him under our guidance and supervision in partial fulfillment of the regulations of the TamilnaduDr.M.G.R Medical University, Chennai. I forward this to the TamilnaduDr.M.G.R Medical University, Chennai, Tamilnadu, India.

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DECLARATION

I solemnly declare that the dissertation entitled "**A Study on Diagnostic approach and management strategies of Invasive fungal sinusitis "** is done by me at Madras Medical College, Chennai-3 during November 2014 to September 2016 under the guidance and supervision of **Prof DR.M.K.RAJASEKAR M.S, DLO.,** to be submitted to The Tamil Nadu Dr.M.G.R Medial University towards the partial fulfillment of requirements for the award of M.S DEGREE in **OTORHINOLARYNGOLOGY,** BRANCH-IV.

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ABBREVIATIONS

AIFS	:	Acute invasive fungal sinusitis
CIFS	:	Chronic invasive fungal sinusitis
CGFS	:	Chronic granulomatous fungal sinusitis
DNE	:	Diagnostic Nasal Endoscopy
PNS	:	Paranasal Sinuses
HPE	:	Histopathological Examination
DCLD	:	Decompensated Liver Disease
DM	:	Diabetic Mellitus

INDEX

S.No	Content	Page No
1.	Introduction	1
2.	Mycology	10
3.	Diagnostic Approach	16
4.	Treatment	30
5.	Aims & Objectives	41
6.	Materials & Methodology	42
7.	Observations	44
8.	Review of Literature	63
9.	Discussion	67
10.	Conclusion	75
11.	Annexure Bibliography Proforma Master Chart Information Sheet Patient Consent Form Ethical Committee Clearance	

INTRODUCTION

In 1791 first description about fungal sinusitis was made by plaignand.

The upper airway mucormycosis was first explained by Paultauf in the year 1885 and also he coined the term mycosis mucorina. Now it is popularly called as mucormycosis.[1]

Mackenzie in the year 1893 gave aspergillus to be the cause. Granulomatous fungal sinusitis was reported by Wright in 1927[2]. Aspergillus flavus was isolated in most of the cases of granulomatous fungal sinusitis in Sudan. In 1943 three fatal cases of rhinocerebral mucormycosis, ophthalmoplegia and proptosis was described in patients having diabetic ketoacidosis.[3] In 1955, the first cure of mucormycosis was reported by Harris.[4] In 1956 with the invention of Amphotericin B for the treatment of mucormycosis dramatically decreased the mortality of the disease

In 1965, clinical presentation of invasive and non invasive forms of aspergillosis was described by Hora.[5.] The non invasive form was found to have thick, darkish greasy material which upon removal produces good prognosis. Invasive form is very rare and presented with pain and mass that mimics malignancy. McGill et al

described a classification consisting of three types namely Indolent aspergillosis, aspergilloma and sinus aspergillosis.[6] Indolent aspergillosis was described when unilateral maxillary sinusitis failed to respond to antibiotic therapy.

First treatment considered was to remove the affected mucosal lining of the sinuses. Later McGill described a new entity in immunocompromised patients as fulminant aspergillosis. This was considered similar to rhinocerebral mucormycosis and was treated by amphotericin B and surgical debridement.

In 1983 allergic aspergillus sinusitis was described by Waxman with history of nasal polyps and allergic rhinitis.[7] This was mistaken for invasive fungal sinusitis later they observed increased Ig E level and increased sensitivity to fungal antigens.[8]

The term fungal ball (mycetoma) was previously described as sinus aspergilloma. It has been proven that the chronic invasive fungal sinusitis has high rate of recurrence, persistence of disease and poor prognosis.[9] DeShazo described chronic invasive form into two types based on histopathological examination onto granulomatous and non granulomatous form.[10]

"There are three types of invasive forms namely

1) Acute fulminant invasive fungal sinusitis

2) Chronic invasive fungal sinusitis

3) Granulomatous invasive fungal sinusitis.[10]"

Chronic invasive fungal sinusitis and granulomatous invasive fungal sinusitis are characterized by a prolonged clinical course with slow disease progression, sinusitis on radiologic imaging, and histopathologic evidence of hyphal forms within sinus mucosa, submucosa, blood vessel, or bone.

The clinical presentation of the two subtypes can be similar. For this reason and for clarity the term chronic invasive funal sinusitis was used. Distinguishing features of granulomatous and nongranulomatous subtypes are indicated when appropriate. Presently the presence or absence of a granulomatous response does not alter the prognosis or the therapeutic intervention.

.The mainstays of therapy are reversal of the source of immunocompromise, systemic high dose amphotericin B and surgical debridement of nonviable tissue. In diabetic patients, the survivorship ranges from 60% to 90%,whereas in leukemic patients and those in whom the source of immunocompromise is not readily reversible, survivorship in 20-50 %[10]

FUNGAL SINUSITIS CLASSIFICATION

Non invasive/Extramucosal[11]

Fungal ball

Allergic fungal rhinosinusitis (AFRS)

INVASIVE

Acute / fulminant

Chronic invasive

a.Non granulomatous

b.Granulomatous

INVASIVE FUNGAL RHINOSINUSITIS

It is most common in immunodeficient people

65% - hematological malignancy

23% - diabetic mellitus

7% - long term steroid therapy

2% - HIV

Others – transplant patients

In general mucormycosis is most common than aspergillus species which is more common in diabetics.[12]

ACUTE INVASIVE FUNGAL RHINOSINUSITIS (AIFS)

AIFS takes a rapid course. It is suspected when patient presents with fever (most common- 50-90%)[13]of unknown origin not responding to broad spectrum antibiotics for 48 hrs, localization of symptoms to nose or PNS such as orbital swelling, facial pain or nasal congestion. Orbital signs are proptosis, ophthalmoplegia, visual loss in 50% of cases.[12] Among immunosupressed patients Scedosporium apiospermum, fusarium, pseudallescheria boydii species becomes invasive.Some organisms usually pseudoallescheria boydi resistant to amphotericin b.

Before 1 Week

After 1 Week

CHRONIC INVASIVE FUNGAL SINUSITIS (CIFS):

It can occur both in immunocompromised and competent people and slowly progressive with prolonged course.[12] CIFS is associated with high rate of recurrence and persistent of disease. CIFS is divided into two types.

Granulomatous form

Non granulomatous form

Clinical presentation of these two types may be similar. Granulomatous form usually occurs in immunocompetant people and non granulomatous in immunosuppressed. The presence or absence of granulomatous response does not alter the progress or therapeutic intervention.

Symptoms related to invasive disease may take months or years to develop involving orbit or skull base.

Invasion into the orbit from PNS - proptosis which is most common presentation of granulomatous disease.

Invasion of maxillary floor – palatal erosions

Erosion of cribriform plate - chronic headache, seizures, decreased mental status or facial neurological deficits.

Extension to sphenoid sinus – orbital apex syndrome or cavernous sinus syndrome.

Extension into pterygopalatine fossa – cranial nerve deficits.

Other complications – mycotic aneurysm, internal carotid artery rupture, cavernous sinus thrombosis.

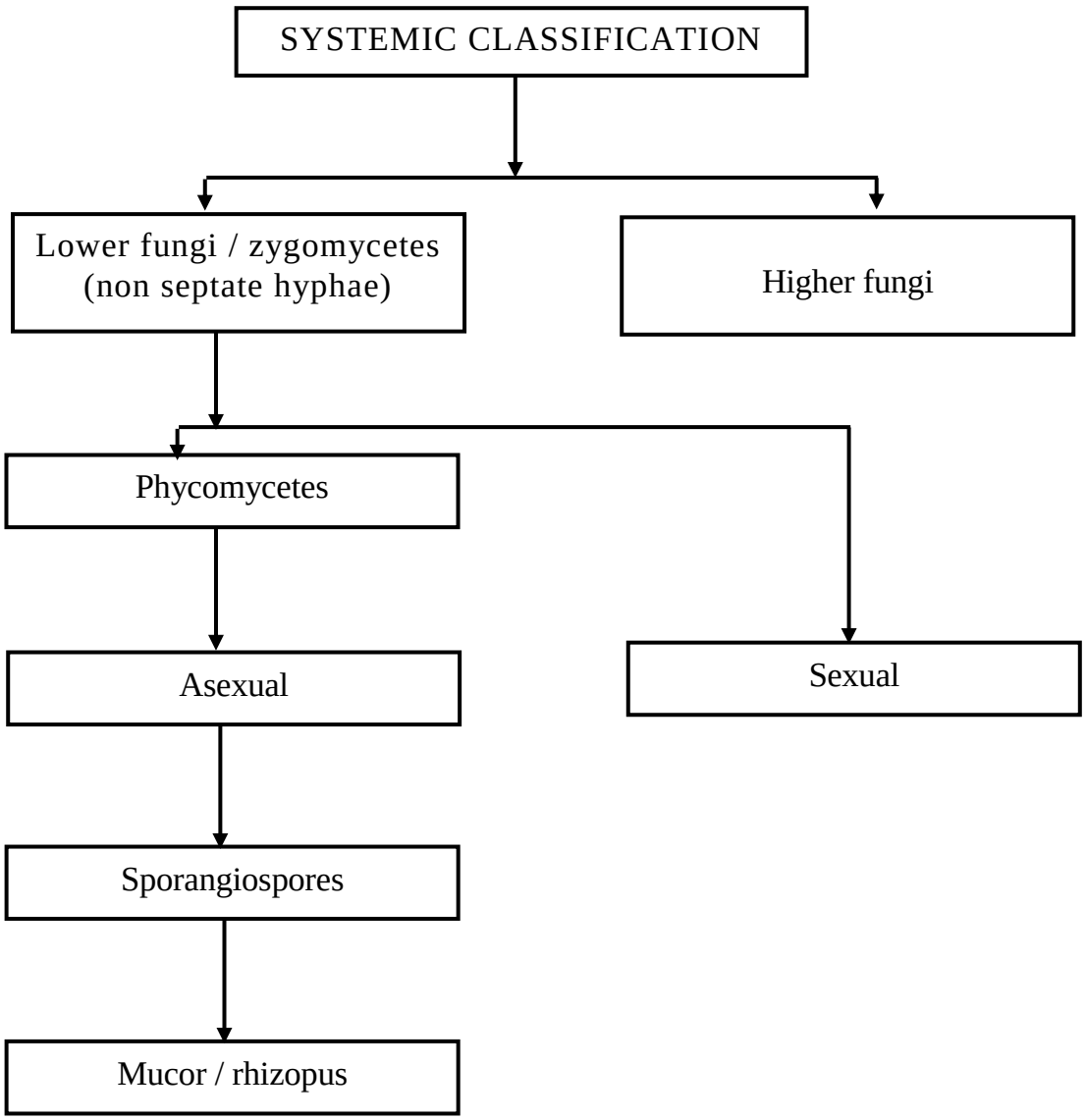
In chronic invasive fungal sinusitis, aspergillus were identified as most common organism. Others like Mucor, alternaria, curvularia, candida, bipolaris, dreschleria, sporothrix, schenchi, pseudoallescharia boydii can also be involved.

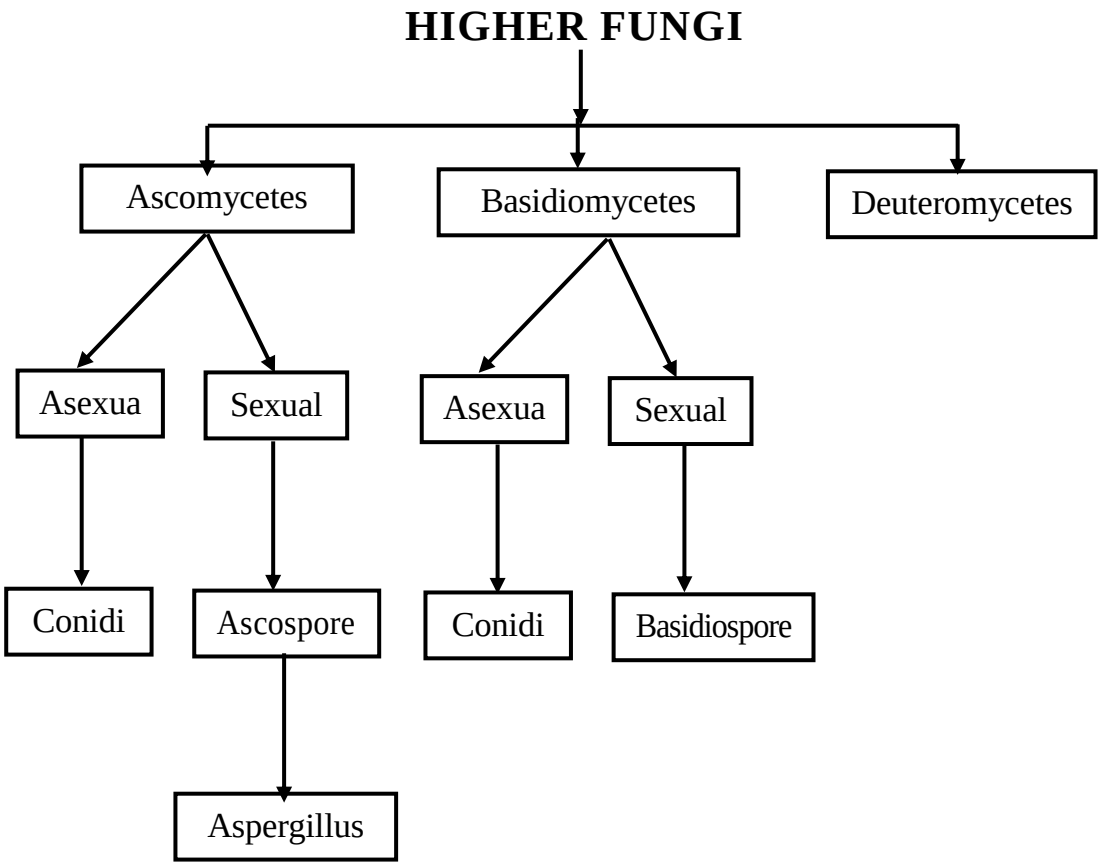
“Chakrabarti study showed that among patients with aspergillus causing invasive disease, 29% with granulomatous type had cutaneous type 4 hypersensitivity to aspergillus antigen compared to non granulomatous type in which none showed type 4 reactions.”

Deshazo has emphasized that all cases of non granulomatous type occurred in diabetics.

Granuloma is formed by presence of indigestible organisms and cell mediated immunity against inciting agent.

FUNGAL CLASSIFICATION




HIGHER FUNGI
Ascomycetes
Basidiomycetes
Deuteromycetes
Asexua
Sexual
Asexua
Sexual
Conidi
Ascospore
Conidi
Basidiospore
Aspergillus

MYCOLOGY

MUCORMYCOSIS

"Mucormycosis is a disease caused by mucorales like Rhizopus, rhizomucor, mucor, absidia, cunninghamella species etc.., most common and virulent species is Rhizopus oryzae"[12].

Mucor causes vascular invasion and obliteration that leads to ischemic necrosis.

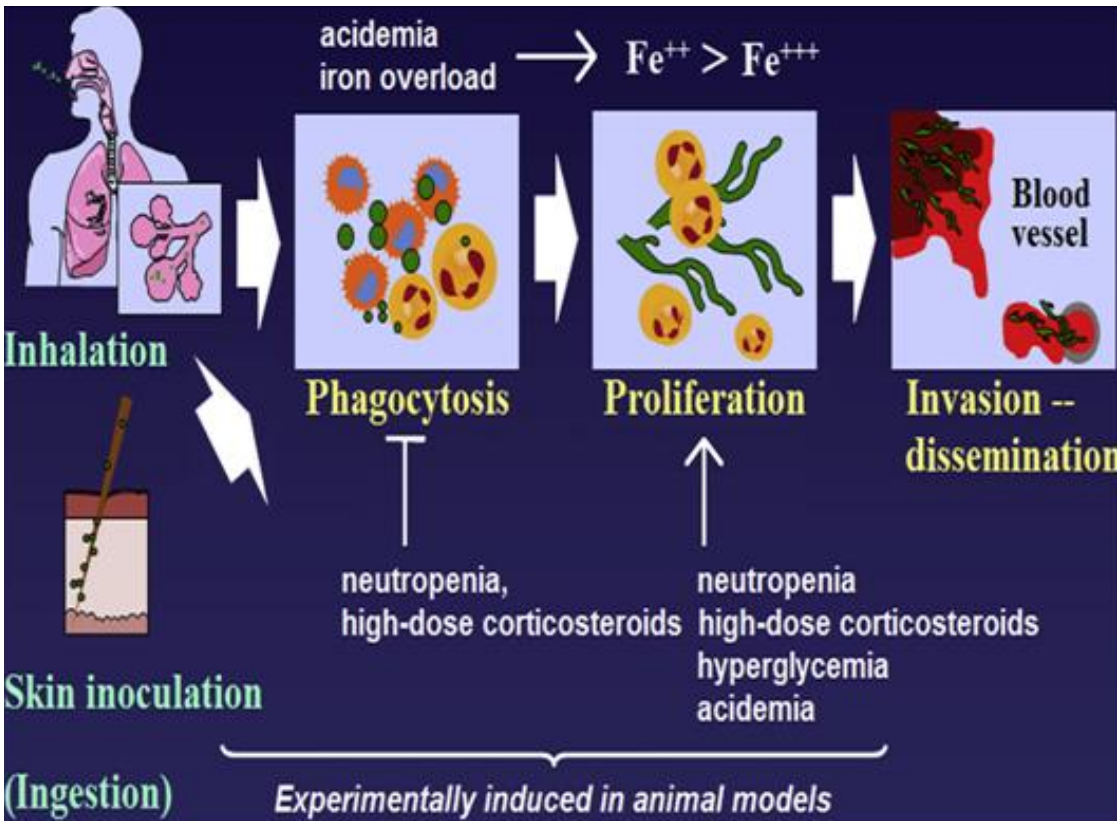
Iron is essential for rhizopus growth. Since iron is strongly bound to transferrin, normal human serum can inhibit the growth of Rhizopus but in diabetics and DKA due to increased free iron and low pH promotes its growth.[12] Increased susceptibility in hemodialysis patients is due to ability of the mucorales to extract iron from desferroxamine.

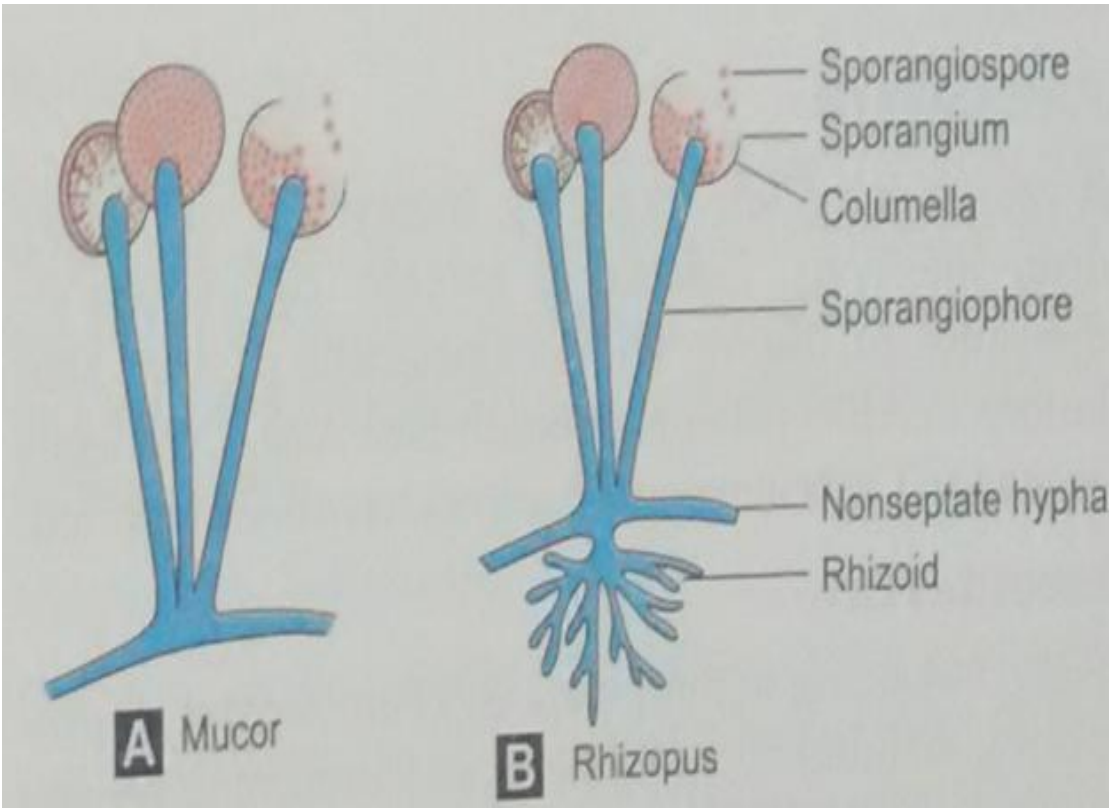
PATHOGENESIS

"Primary mode of spread is through inhalation of fungal spores. Small spores of mucorales (3 – 11um) reach up to distal alveolar spaces causing sinopulmonary mucormycosis.[14,16] Large spores (>10um) may lodge in the nasal turbinates causing sinusitis. To affect human, fungal spores generally overcome phagocytosis by macrophages and neutrophils and germinate into hyphae".[14,15]

In chronic steroid users impairment of macrophage migration, ingestion, phagolysosome fusion, chemotaxis occurs causing loss of fungicidal activity against mucorales.

Recently it is found that sporangiospores are able to adhere to subendothelial matrix proteins and invade intact endothelial barriers. Rhizopus secretory component can be toxic to endothelial cells. Therefore both spores and mycotoxins produced indirectly by endosymbiotic bacteria influence the virulence of molds causing mucormycosis[5].





DIFFERENCE BETWEEN MUCOR AND RHIZOPUS

1) Rhizopus has rhizoid and is absent in mucor.

2) Sporangiospores of mucor arises randomly from along the aerial mycelium whereas sporangiospores of rhizopus arises from rhizoid.[17,18]

ASPERGILLUS

Among Aspergillus commonly isolated species are A fumigatus, A flavus, A niger, A terralis[19].

In US most common species isolated in invasive disease is A fumigatus.

Where as in India it is A flavus.[12]

A flavus is most commonly associated with CIFS but it also causes chronic granulomatous fungal disease.

These organisms most commonly found in food, air, soil and water. According to differences in temperature, humidity and precipitation it acts as environmental burden.

HOST SUSCEPTIBILITY

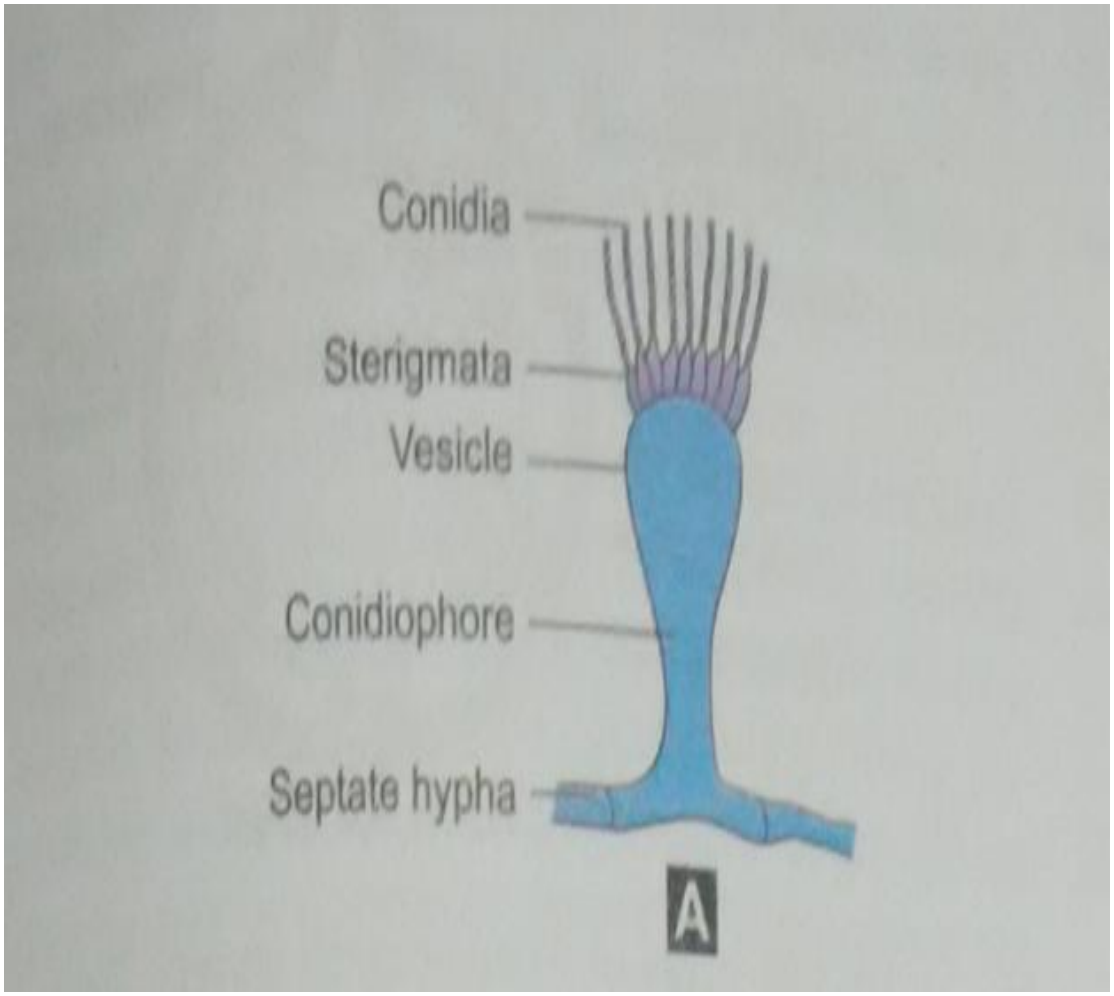
“Inhaled conidia affect both innate and adaptive immune responses.

Conidia interact with leukocytes and epithelial cells within the respiratory tract following hyphal invasion with endothelial cells. Neutrophils have little inflammatory response. Conidia (not hyphae) bind the host soluble receptor pentraxin-3 via GM and this reaction increases the uptake by alveolar macrophages, dendritic cells, and drives the Th1 immune response. Invasive chronic sinusitis is characterized by

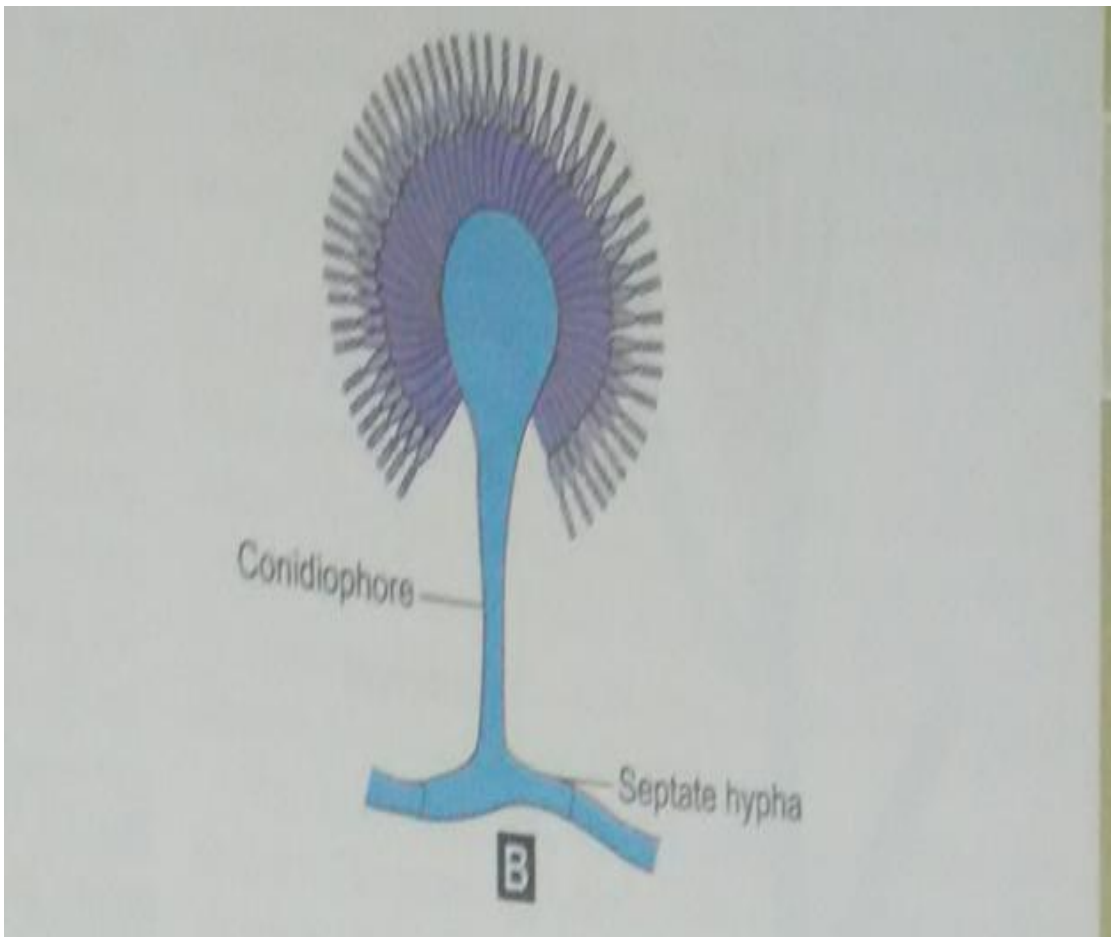
pain, facial swelling, purulent rhinorrhoea, nasal obstruction. It is commonly localized to one sinus and due to direct invasion involves surrounding cranial nerve"[19].

It causes angioinvasion but does not cause obliteration of vessels like mucormycosis.[12] In cerebral involvement hemorrhagic infarct may be seen.

ASPERGILLUS FLAVUS



ASPERGILLUS FUMIGATUS



DIAGNOSTIC APPROACHES:

DIAGNOSTIC NASAL ENDOSCOPY (DNE)

DNE should be done on all immunocompromised patients with fever of unknown origin for more than 48 hours.

FINDINGS

Most common and consistent findings are nasal mucosal ulceration, discoloration and granulation.

1) Mucosal abnormalities are

   a. Middle turbinate 67%

   b. Septum 24%

   c. Palate 19%

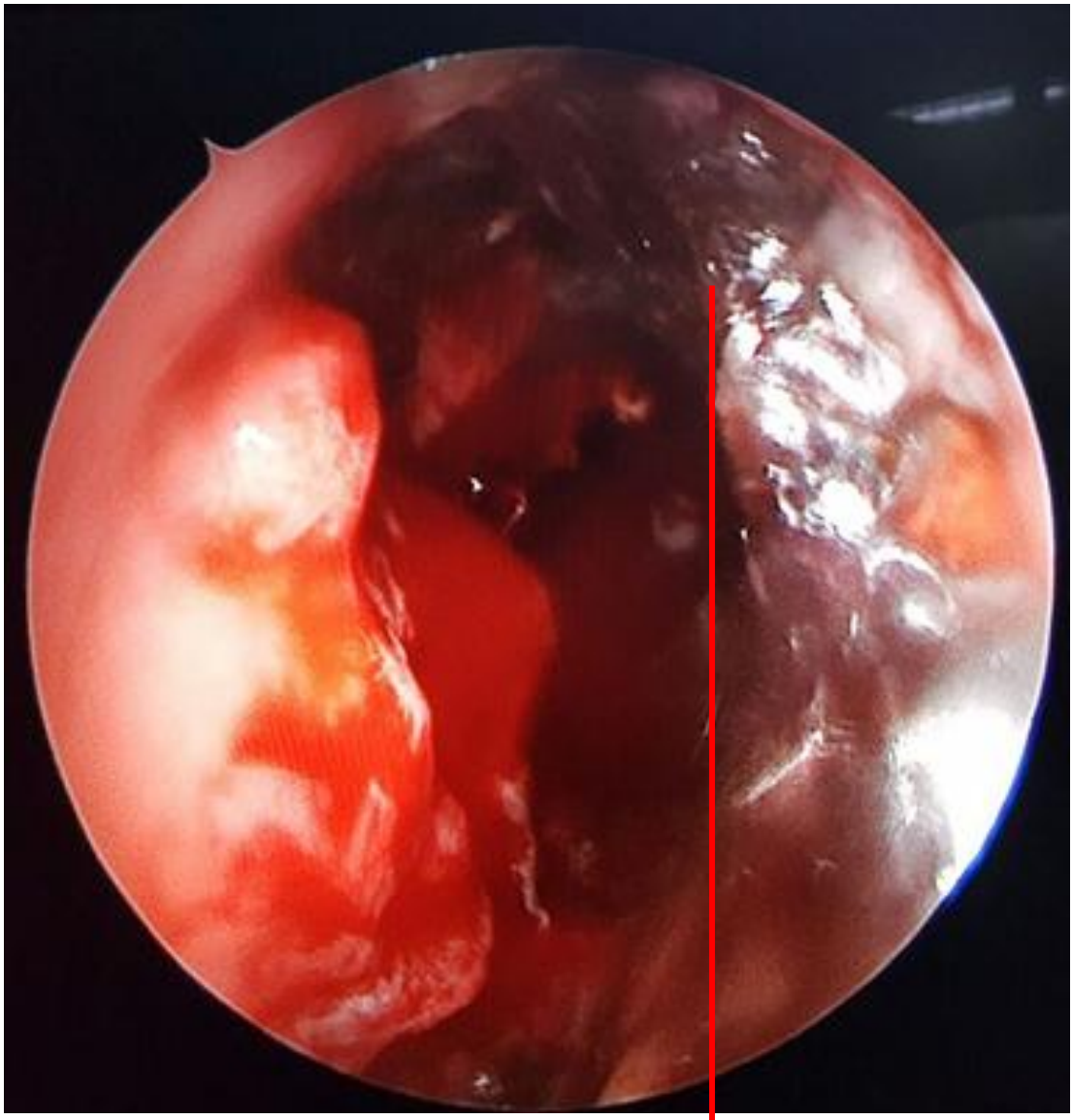
   d. Inferior turbinate 10%

2) Decreased sensation, decreased mucosal bleeding

3) Black necrotic debris in nasal cavity or palate

Frank necrosis may give false negative results.MT biopsy results 100% specificity, 75% sensitivity in AIFS.[13]

DNE OF MUCORMYCOSIS



Necrotic debris involving the septum

PALATAL INVOLVEMENT OF MUCORMYCOSIS

Black Crust

HISTOPATHOLOGICAL EXAMINATION (HPE)

Histopathologic evaluation of tissue biopsies is required to confirm the diagnosis of invasive fungal rhinosinusitis.

“ Fungal disease is determined to be invasive if it meets the following criteria on histopathologic examination

1) hyphal forms within the submucosa with or without angiocentric Invasion

2) Tissue necrosis with minimal host inflammatory cell infiltration”.

Ideally, tissue should be sent for frozen and permanent sections. Frozen section allows for a timely diagnosis, whereas permanent section with Gomori-methenamine silver stain confirms the diagnosis and provides important morphologic information that may be helpful in determining the fungal species

MUCORMYCOSIS

“Definitive diagnosis of mucormycosis requires evidence of fungal invasion. Tissue Hyphae of the Mucorales are broad (3–25 um), thin-walled, mostly aseptate, with nondichotomous, irregular branching, occasionally at right angles[20] and sometime shows twisted and compressed hyphae, which may be mistaken for septae, similar to Aspergillus”.

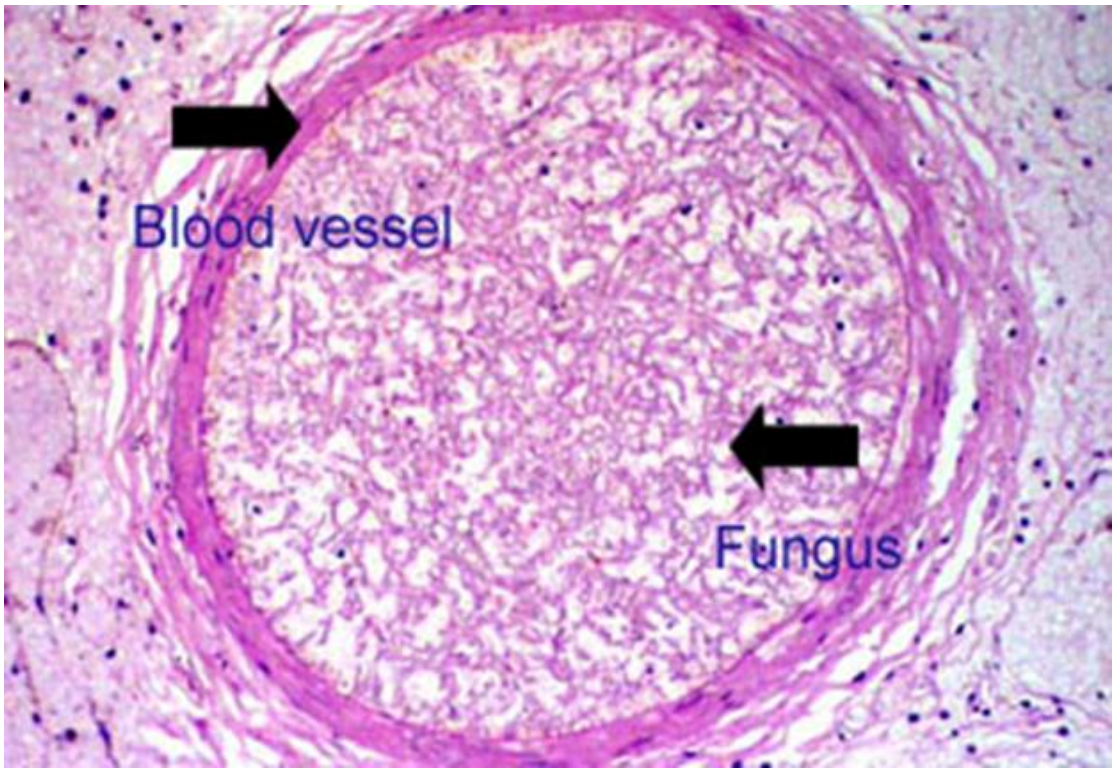
Perineural invasion, which is found in 90% of tissues that contain nerves, can be a useful diagnostic clue.

Once invasive organism shows a marked predilection for vascular invasion, it directly invades the walls of large and small arteries and sometimes veins, causing thrombosis.

This contributes to the necrotic ischemic appearance which is characteristic of advanced disease.

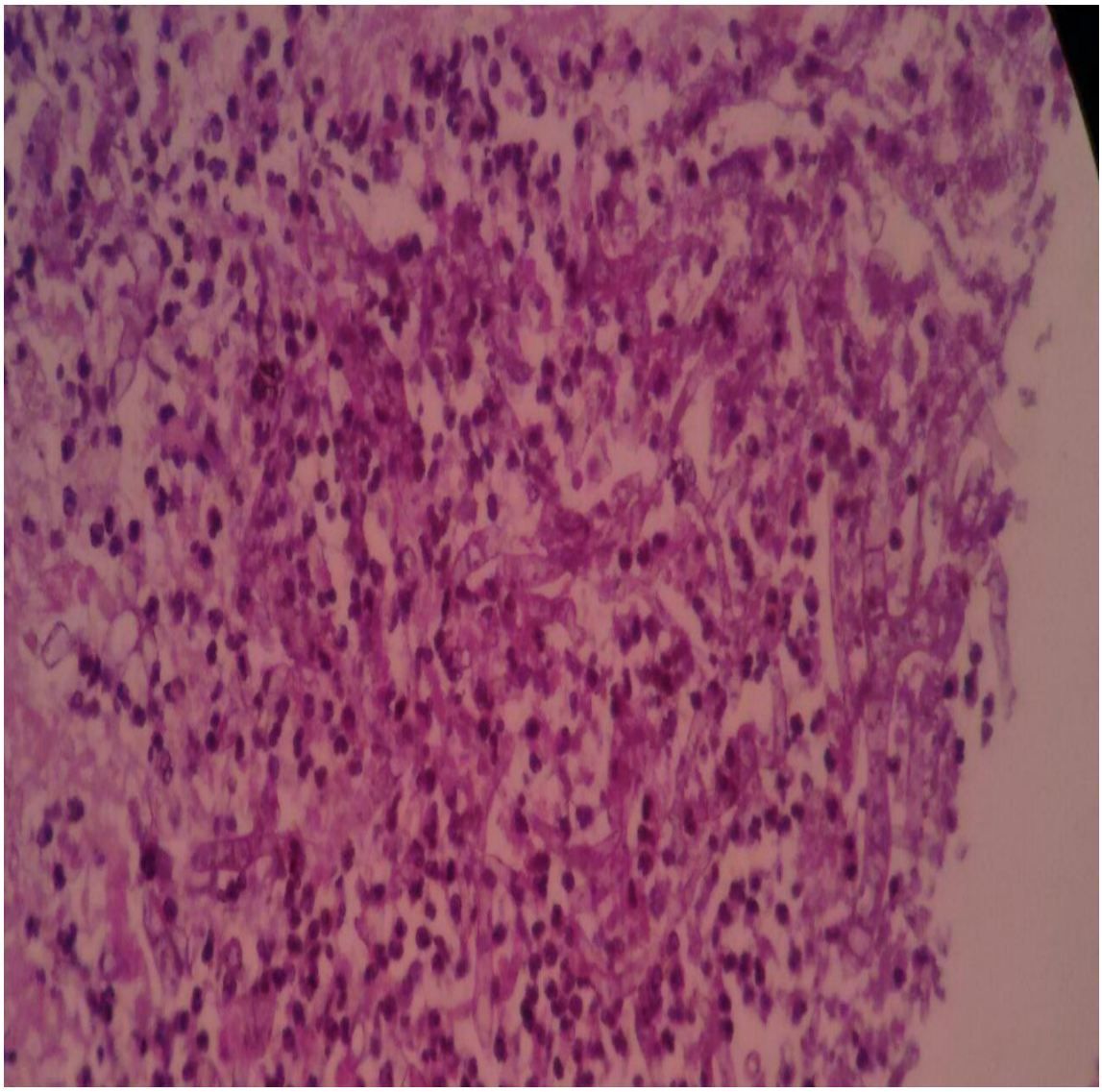
Inflammatory tissue reaction is variable and reflects the host's immunologic status. Usually edema and necrosis with accumulations of neutrophils, plasma cells, and sometimes giant cells are seen.

ANGIOINVASION

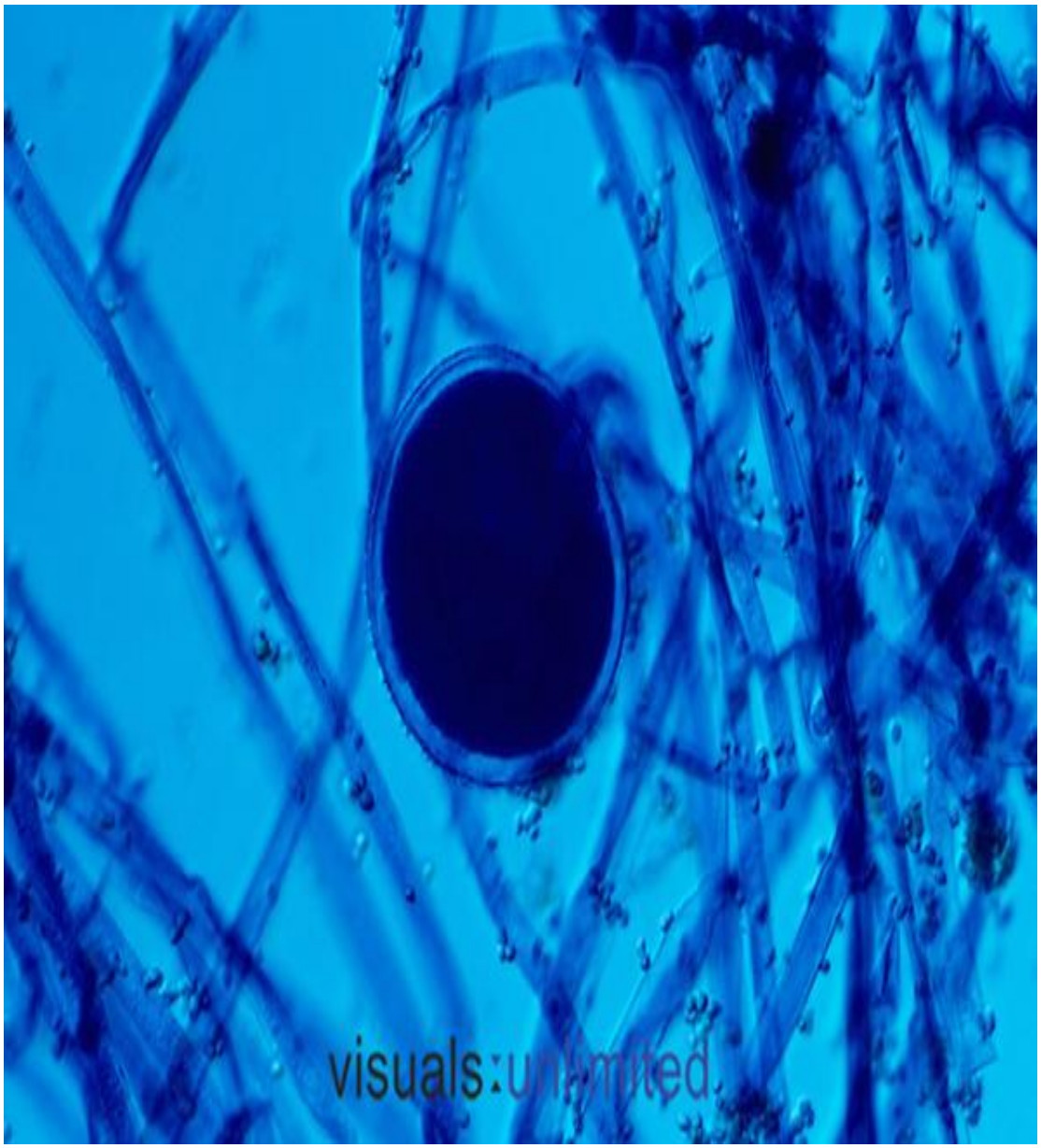


FUNGAL STAIN SLIDE

HISTOPATHOLOGICAL EXAMINATION:



CULTURE:



ASPERGILLUS

It is described that gross appearance of granulomatous chronic invasive fungal rhinosinusitis as firm, hard, rubbery, fibrous, grayish white masses with an irregular surface.

Microscopically it is described that *Aspergillus* hyphae are narrower, regular, frequently septated, and branch at 45°.

"Periarterial inflammation without direct involvement of fungal elements and no true vascular invasion were noted.

It is classified into three variants

ii) proliferative (granulomatous pseudotubercles in a fibrous tissue stroma),

iii) Exudative-necrotizing (with prominent foci of necrosis),

iv) Mixed form".

Granulomatous chronic invasive fungal rhinosinusitis as granulomas composed of eosinophilic material surrounded by fungus, giant cells, and palisading nuclei, variable numbers of lymphocytes, and plasma cells.[20]

Nongranulomatous chronic invasive fungal rhinosinusitis was characterized by tissue necrosis with little inflammatory infiltrate and dense hyphal accumulation resembling a fungus ball (mycetoma). The

fungi in this form may breach mucosal barriers to invade blood vessels or simply cause an arteritis without vascular invasion, although both granulomatous and nongranulomatous may result in tissue necrosis.

ASPERGILLUS VS MUCOR

CULTURE:

Sample for Culture can be taken from

Necrotic debris

Slough covering the nasal cavity

Crust

Purulent secretions in sinuses

Nasal swab for fungal culture can be insufficient

Alternatively aspirate from the irrigation of maxillary sinus with small amount of saline can be used for fungal stain by KOH mount.

RADIOGRAPHY

CT PNS is most commonly used imaging to evaluate suspected patients of invasive fungal rhinosinusitis.

Fine 2mm cut scan in both axial and coronal view is required.

"Clue to diagnosis are focal or diffuse areas of hyper attenuation within a sinus fungal colonization, thick mucin plugs, infection and AFS. It is important to note that both chronic invasive fungal rhinosinusitis and AFS can cause bone erosion or expansion, suggesting a potentially invasive process. It is noted that soft tissue infiltration of periantral fat planes around the maxillary sinus provides early evidence of invasive fungal rhinosinusitis in the appropriate Clinical setting"[13]

ADVANTAGES

1) Its ability to define bony architecture makes it as imaging of choice for invasive fungal sinusitis.

2) Confirm the presence of sinusitis and type of sinus involved.

3) Bony architecture variations can be noted.

4) May show features suggestive of invasive fungal disease

DISADVANTAGES

CT findings are non specific.[12]

1) It cannot be correlated well with pathological and surgical findings.

2) In the author series 12% of invasive fungal sinusitis patient have a normal study in CT PNS.

CT PNS

CT PNS shows extensive inflammation with bony erosions in the maxillary, ethmoid and sphenoid sinuses probably fungal etiology suggesting culture and sensitivity correlation.

MAGNETIC RESONANCE IMAGING (MRI) OF BRAIN

MR imaging is useful for assessing dural involvement and intradural extension of disease."

ADVANTAGES

1) It is superior to CT to see the extent of intracranial and intra orbital invasion like orbital apex syndrome, seizures, stroke. Mortality rate is high in patient with intra cranial extension.

2) MR imaging scan can prevent unnecessary procedures in which patients are unlikely to undergo surgery.

MRI BRAIN WITH CONTRAST IMPRESSION

It shows evidence of enhancing lesion seen arising from the sphenoid sinus with infiltration into the adjacent sphenoid bone. Extra dural extension seen into the anterior temporal fossa and anterior right temporal parenchyma.

Above features could suggest possibility of fungal pathology.

Kindly correlate clinically and with HPE findings to rule out malignancy.

TREATMENT

The mainstay of treatment of invasive fungal rhinosinusitis continues to be a combination of antifungal antibiotics, aggressive surgical debridement and treating the underlying cause of immunocompromised state.

Several patients demonstrated good results for surgery in the treatment of invasive fungal rhinosinusitis. The surgical approach to invasive fungal rhinosinusitis has changed over the years secondary to the advancement in endoscopic sinus surgery. Extensive surgical resections in the form of radical maxillectomy and craniofacial resection, are not practiced now because of more use of endoscopic sinus debridement. Radical resections to remove disease outside the sinonasal cavity rarely achieve negative margins or improve long-term survival.

SURGICAL DEBRIDEMENT

Surgical debridement comprises several important goals

1) Progression of the disease is being slowed down that allows time for bone marrow recovery

2) Fungal load is reduced, which decreases the burden on recovering neutrophils

3) It provides a specimen for culture. A portion of all surgical specimens should be cultured to provide epidemiologic information in the event of a fungal outbreak.

Proper specimen must be taken as it provide important data about certain species such as *Pseudallescheria boydii which will not respond to Amphotericin B*[12,]

On all patients with biopsy-proven disease or any patient suspected of having invasive fungal disease early aggressive endoscopic sinonasal debridement should be performed, Surgery should focus on debriding the involved sinuses or structures (i.e., turbinates, septum) up to bleeding margins of healthy mucosa seen.

MEDICAL MANAGEMENT

CONCEPTS AND PRINCIPLES

"Medical advances have led to increased numbers of immunocompromised patients.

1) There has been improvement in education on antifungal therapy in the medical community.

2) Better control methods for underlying diseases (i.e., highly active antiretroviral therapy, reduction in chemotherapy-induced

neutropenia, more options for anti rejection therapies) have been developed.

3) Identification of specific risk factors or groups continues to be identified.

4) Standardized antifungal susceptibility testing for yeasts is now available for clinical decision

5) Safe triazoles (fluconazole and itraconazole)[21] have demonstrated a positive impact for antifungal prophylaxis, empiric, and therapeutic strategies.

6) Improvements in the formulations of amphotericin B have produced a less toxic product.[21]

7) Some important pivotal clinical studies in mycoses management has been completed.

8) There continues to be enthusiasm in the pharmaceutical industry to identify new antifungal targets and drugs".

ANTIFUNGAL TREATMENT PRINCIPLES

- "Correct identification of the fungus is essential.
- Use of standard, published antifungal regimens depends on fungus identified and clinical syndrome.

- Clinician should consider initial therapy as an induction phase with optimization in both dose and antifungal drug, which gives maximum fungicidal activity at the site of infection; consider combination therapy in certain cases.

- Control of the underlying medical or immunosuppressive conditions is mandatory.

- Clinician must pay particular attention to drug interactions, pharmacokinetics, and resulting toxicities; this may require measurement of drug levels in certain circumstances.

- After apparent stabilization of clinical symptoms and signs of infection with treatment, consideration of a consolidating drug regimen in dose or drug to complete a defined course of therapy is required.

- Follow-up for relapse/reinfection after treatment should be at least 6 months to a year depending on fungus and type of infection."

PHARMACOLOGY

AMPHOTERICIN B

High-dose Amphotericin B (greater than 1.25 mg/kg per day) is an important adjunct in the treatment of invasive fungal rhinosinusitis.

A full course of Amphotericin B involves a total dose of 2 grams or greater."

MECHANISM OF ACTION

The antifungal activity of amphotericin B is caused by its ability to bind preferentially to ergosterol, a major component of the fungal cell membrane.

Cell membrane permeability is increased following attachment of this lipophilic structure to the fungal cell wall, with leakage of intracellular components and ultimately cell death.[21,22]

Unfortunately, amphotericin B also binds to a lesser degree to cholesterol in mammalian cell membranes, which probably accounts for its toxic effects on human cells. Furthermore, amphotericin B and its interaction with host cells also can have a positive effect by activation of macrophages through an oxidation-dependent process.

DOSAGE

Since Amphotericin B produces hypersensitivity reactions, a test dose (l mg in 50 mL of 5% dextrose over 20 minutes) to be given before the administration of the first full dose of amphotericinB.

During this time, vital signs are monitored for any potential reactions to this agent.

The dose of amphotericin B is not modified for patients with renal insufficiency. Alternative regimens in such patients, however, have included the use of alternate daily dosing (i.e., every other day dosing of twice the usual daily target dose).

COMPLICATIONS

Infusion related reactions: Infusion-related reactions are acute in onset and extremely common in individuals receiving amphotericin B. Symptoms are characterized most commonly by fever, chills, rigors, headache, nausea, malaise, and generalized aches.[22]

Nephrotoxicity: Nephrotoxicity may occur in 80% of patients receiving amphotericin B therapy and is characterised by azotemia, electrolyte wasting (K+and Mg2+) and decrease in urinary concentrating ability. The mechanism by which this occurs is not well-defined. Renal tubular acidosis has also been associated with amphotericin B therapy.

Although renal dysfunctions has been said to be reversible even after high cumulative doses, persistent renal dysfunction was documented among them. Particularly patients receiving a total dose greater than 4 to 5 g of amphotericin B deoxycholate may have permanent renal impairment.

STRATEGY TO AVOID NEPHROTOXICITY:

The approaches to minimize the risk of nephrotoxicity include

1) “Sodium supplementation to maintain intravascular volume and inhibit the tubuloglomerular feedback system. Sodium supplementation can be administered by way of a normal saline bolus, 500 to 1000 mL in adult patients administered before or following the amphotericin infusion."

2) Another strategy is avoiding the use of concomitant nephrotoxic agents.”

Following nephrotoxicity they may develop Anemia (Normochromic, normocytic anemia) with decrease in hemoglobin of up to 35% from baseline has been documented routinely following extended therapy with amphotericin B.

The mechanism is direct suppression of erythropoietin production that may occur in patients with deteriorating renal function. Hemoglobin concentrations usually return to normal within months after therapy is discontinued.

LIPID BASED FORMULATIONS OF AMPHOTERICIN B:

Now a days, lipid-based formulations of amphotericin B has been widely used. Amphotericin B lipid complex (ABLC) amphotericin B cholesteryl sulfate complex (ABCD) and liposomal amphotericin B use a variety of lipid carriers.

The pharmacokinetics of lipid-based formulations of amphotericin B is different from that of amphotericin B deoxycholate.

These lipid-based formulations are preferentially delivered into reticuloendotheliaI tissues, such as the liver and spleen and lesser extent to lungs.[21,22]

The use of lipid-based amphotericin B may be a good alternative for patients who are unable to tolerate the nephrotoxicity associated with amphotericin B deoxycholate or other serious drug interactions with agents such as cyclosporine or tacrolimus. These preparations are probably the drugs of choice for rhinocerebral zygomycosis, that requires administration of high doses of polyenes after surgical debridement. Its reduced toxicity and the other advantages says the

significant expense of these agents in the final outcome of most the disease.

AZOLES: IMIDAZOLES AND TRIAZOLES

Although amphotericin B remains the gold standard for most severe life threatening systemic fungal infections, imidazoles (clotrimazole, ketoconazole, miconazole) and triazoles (fluconazole and itraconazole) second generation triazoles (voriconazole,posaconazole) gives antifungal activity against many fungal pathogens without the serious nephrotoxic effects observed with amphotericin B administration and have been shown to be effective in treatment of systemic mycoses.

MECHANISM OF ACTION

"The azole antifungals (which includes the imidazoles and the triazoles) acts mainly by inhibiting the cytochrome P-450 dependent enzyme lanosterol 14demethylase, which is necessary for the conversion of lanosterol to ergosterol.[22] Ergosterol is a vital component of the cellular membrane of fungi and disruptions in the biosynthesis of ergosterol cause significant damage to the cell membrane by increasing its permeability and ultimately causing cell lysis and cell death.

The antifungal activities of presently used azoles, generally are considered fungistatic and achieve clinical concentrations when tested in vitro. voriconazole more potent against invasive aspergillosis.[22]

SIDE EFFECTS

Triazoles are well tolerated in most patients.

The most commonly documented side effects are

- Gastrointestinal upset, including symptoms such as nausea, abdominal pain, vomiting, and diarrhea.
- rash and headache
- Mild elevations in liver function tests have been reported in approximately 1% to 7% of patients
- Alopecia has been reported
- Doses of itraconazole of 600 mg/d and higher have a relatively high incidence of an aldosterone-like effect with hypertension, hypokalemia, and peripheral extremity edema.
- Peripheral edema of lower legs and feet also can be seen in lower limb
- Visual abnormalities in voriconazole.[22]

TREATMENT OF UNDERLYING DISORDERS OF IMMUNOCOMPROMISED STATE:

- Insulin for diabetic patients and control of glycemic index.
- Immunomodulators for leukemia and neutropenia patients.
- Monitoring of CD 4 count for HIV patients and antiretroviral therapy
- Avoid long term steroids.

AIMS AND OBJECTIVES

1) To assess modes of presentation and complications.

2) To study the appropriate diagnostic approach for early detection

3) To study the various management plans and their efficacy

MATERIALS AND METHODOLOGY

STUDY PLACE

Rajiv Gandhi Government General Hospital, Chennai – 600003.

COLLABORATING DEPARTMENT

Upgraded Institute of Otorhinolaryngology

STUDY DESIGN

Retrospective and Prospective study

STUDY PERIOD

NOVEMBER 2014 to SEPTEMBER 2016

ETHICAL CLEARANCE

Applied for Institutional clearance

INCLUSION CRITERIAS

1) All patients who presents with clinical features suggestive of invasive fungal sinusitis and was subsequently diagnosed as the same

2) Invasive fungal sinusitis with intracranial complications

EXCLUSION CRITERIA

Age below 20 yrs

INVESTIGATION

1) Diagnostic nasal endoscopy and biopsy
2) Fungal culture
3) CT- PNS
4) MRI

DATA COLLECTION

Clinical

BENEFIT TO THE COMMUNITY

1) Early detection of invasive fungal sinusitis

2) To reduce morbidity and mortality

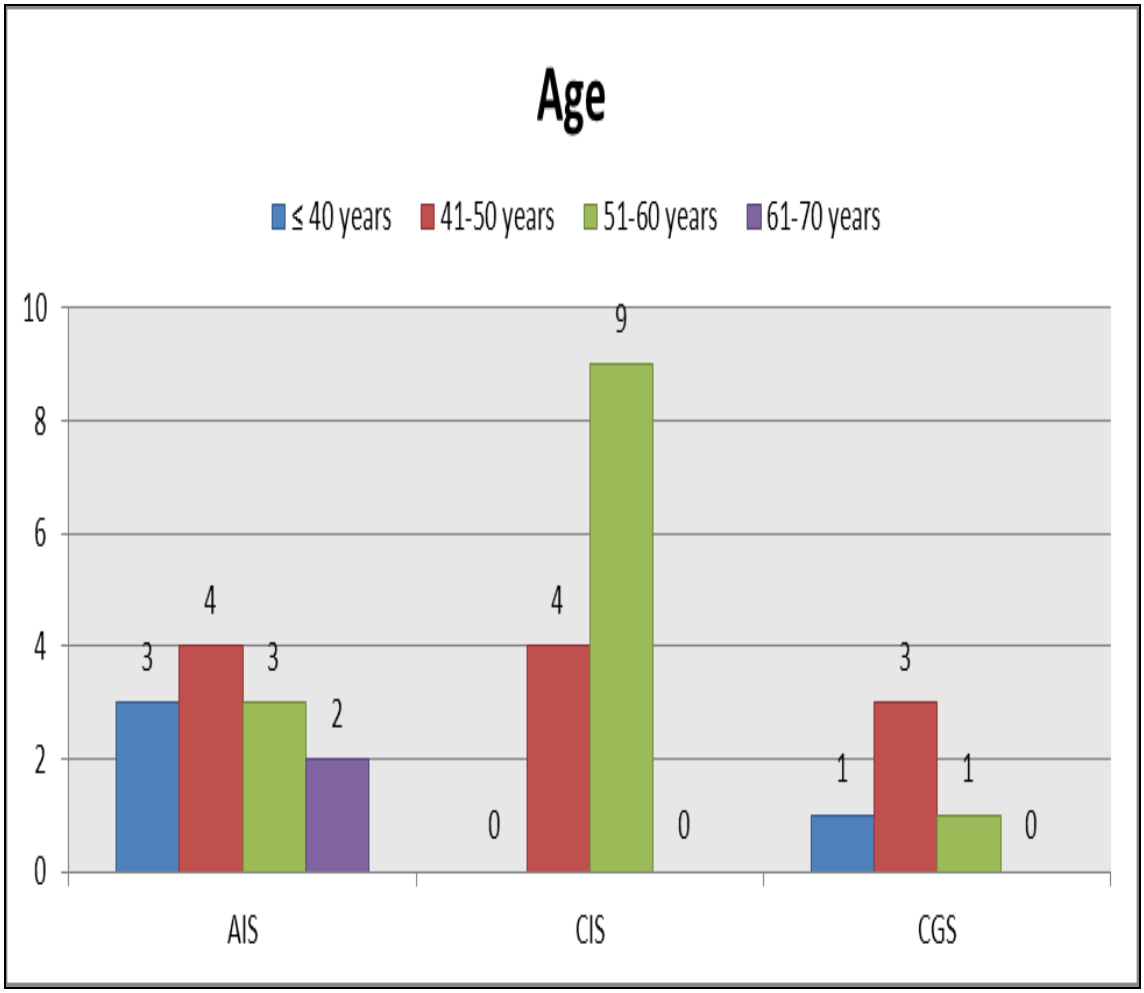
Conflict of interest : nil

Financial support : nil

This is a prospective and retrospective study conducted in our institution from November 2014 to September 2016. All patients who presents with clinical features suggestive of invasive fungal sinusitis included in the study. After clinical examination including routine blood investigations, diagnostic nasal endoscopy biopsy with HPE and culture followed to proceed with imagings like CT PNS and MRI brain was planned if patient presented with complications. Treatment given was debridement and antifungal agents and improving the immunosuppressive state .

OBSERVATIONS

AGE



AIS- ACUTE INVASIVE FUNGAL SINUSITIS

CIS- CHRONIC INVASIVE FUNGAL SINUSITIS

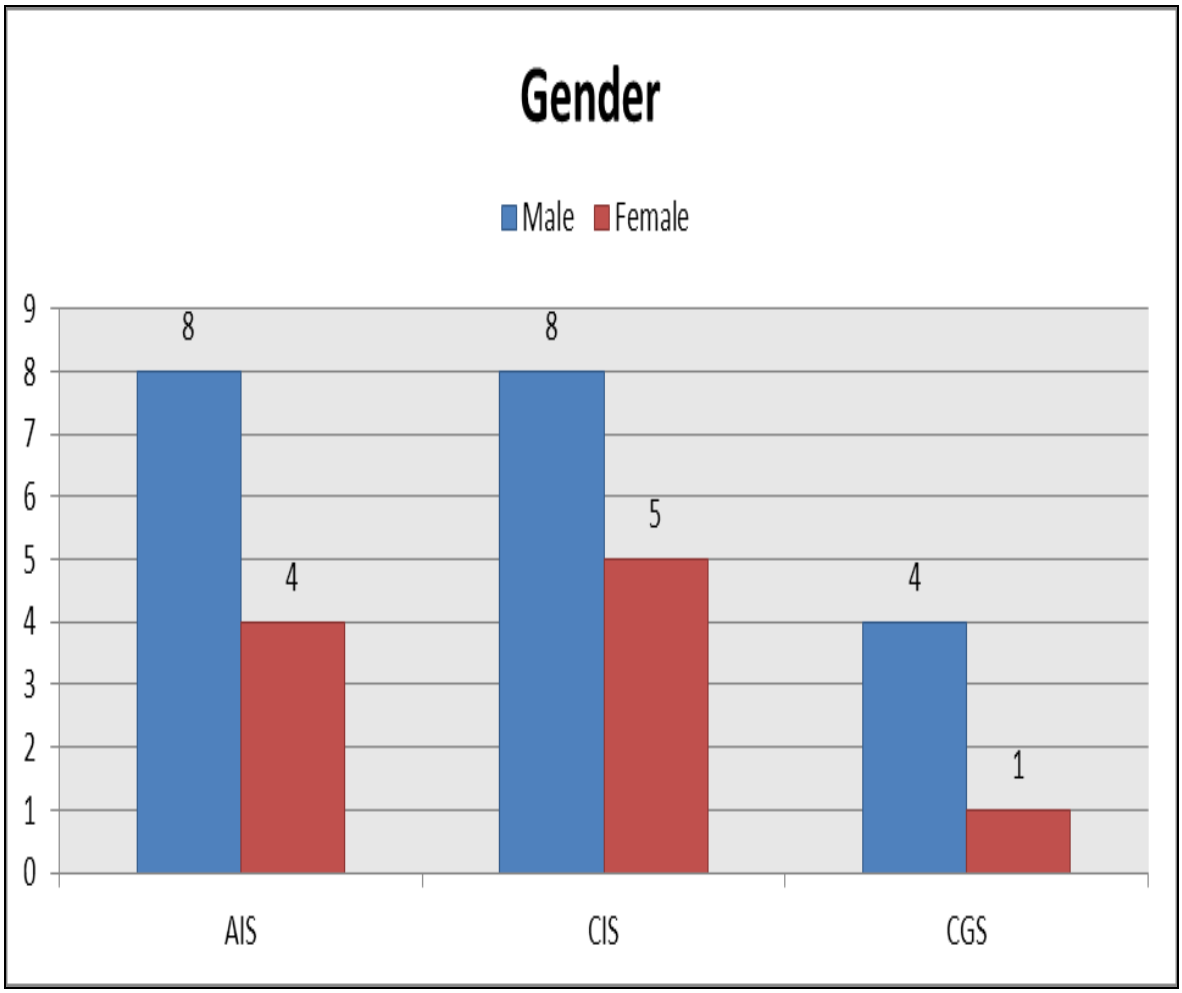
CGS- CHRONIC GRANULOMATOUS FUNGAL SINUSITIS

Age	AIS	CIS	CGS	AIS %	CIS %	CGS %
≤ 40 years	3	0	1	25.00	0.00	20.00
41-50 years	4	4	3	33.33	30.77	60.00
51-60 years	3	9	1	25.00	69.23	20.00
61-70 years	2	0	0	16.67	0.00	0.00
Total	12	13	5	100	100	100

Age Distribution	AIS	CIS	CGS
N	12	13	5
Mean	48.83	53.46	43.40
SD	11.20	4.61	5.41
P value One Way ANOVA			0.0664

In our study among 30 patients mean age : 48

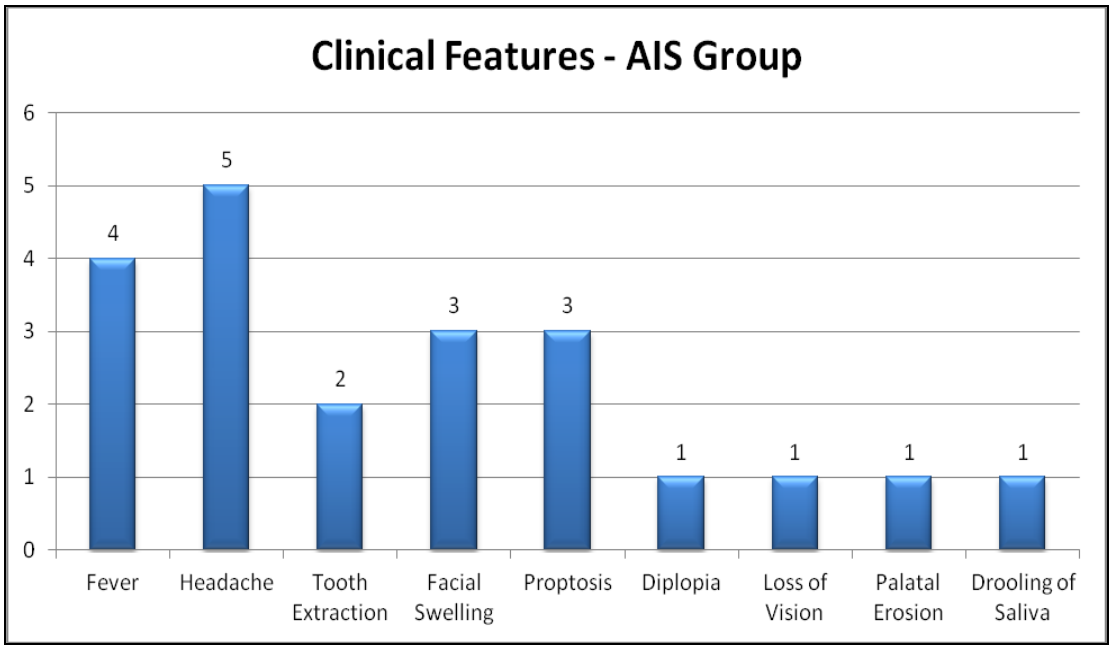
Gender

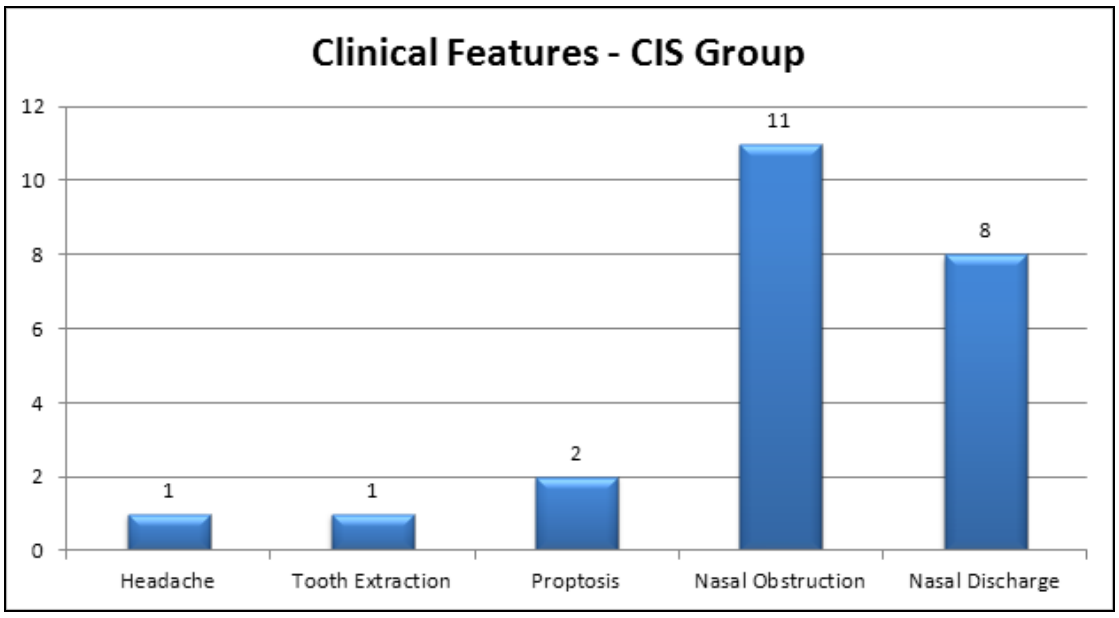


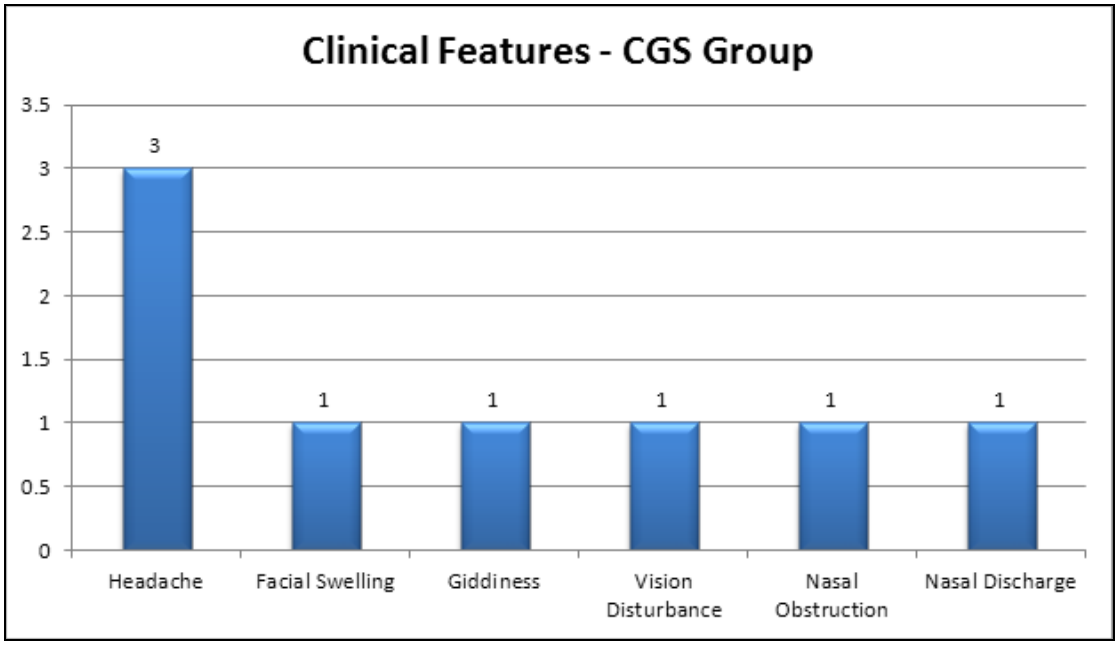
Gender	AIS	CIS	CGS	AIS %	CIS %	CGS %
Male	8	8	4	66.67	61.54	80.00
Female	4	5	1	33.33	38.46	20.00
Total	12	13	5	100	100	100
P value Fishers Exact Test				0.8822		

Male -67%, Female-33%

CLINICAL FEATURES



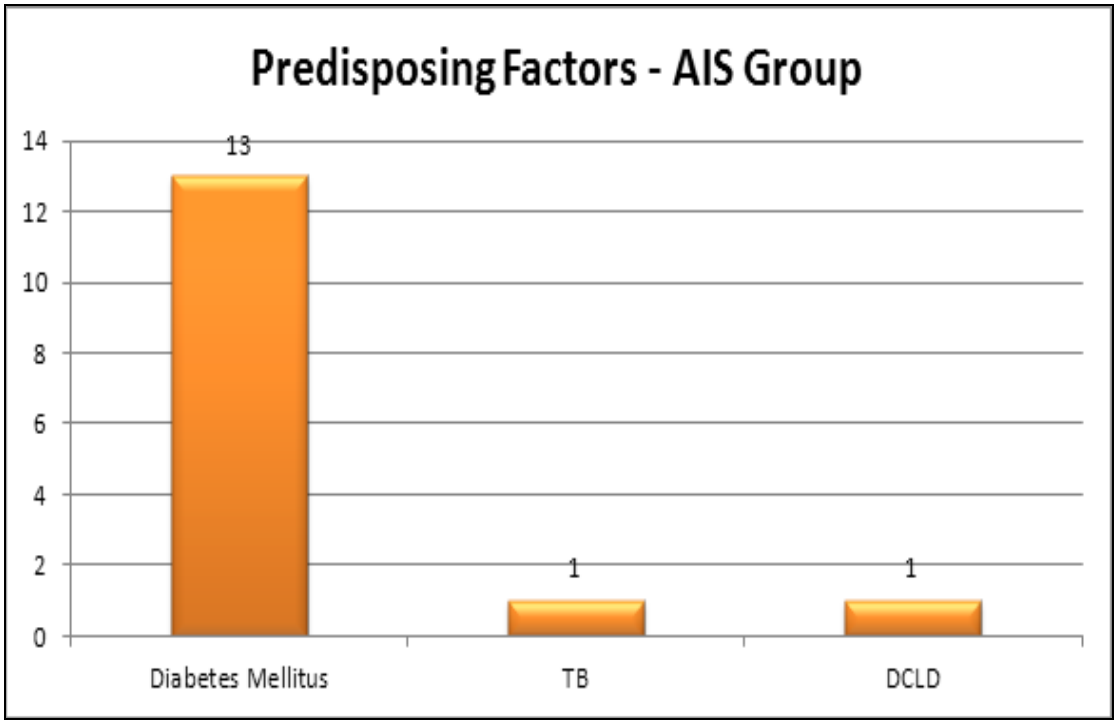


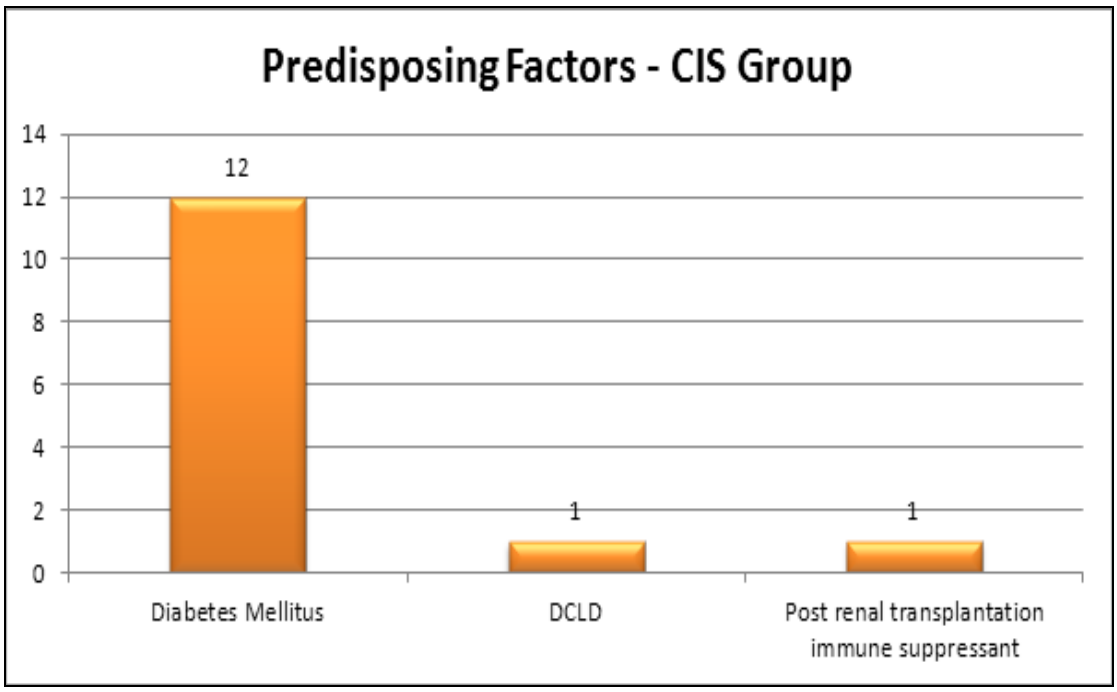

Clinical Features - CGS Group
3.5
3
2.5
2
1.5
1
0.5
0
3
1
1
1
1
1
Headache
Facial Swelling
Giddiness
Vision Disturbance
Nasal Obstruction
Nasal Discharge

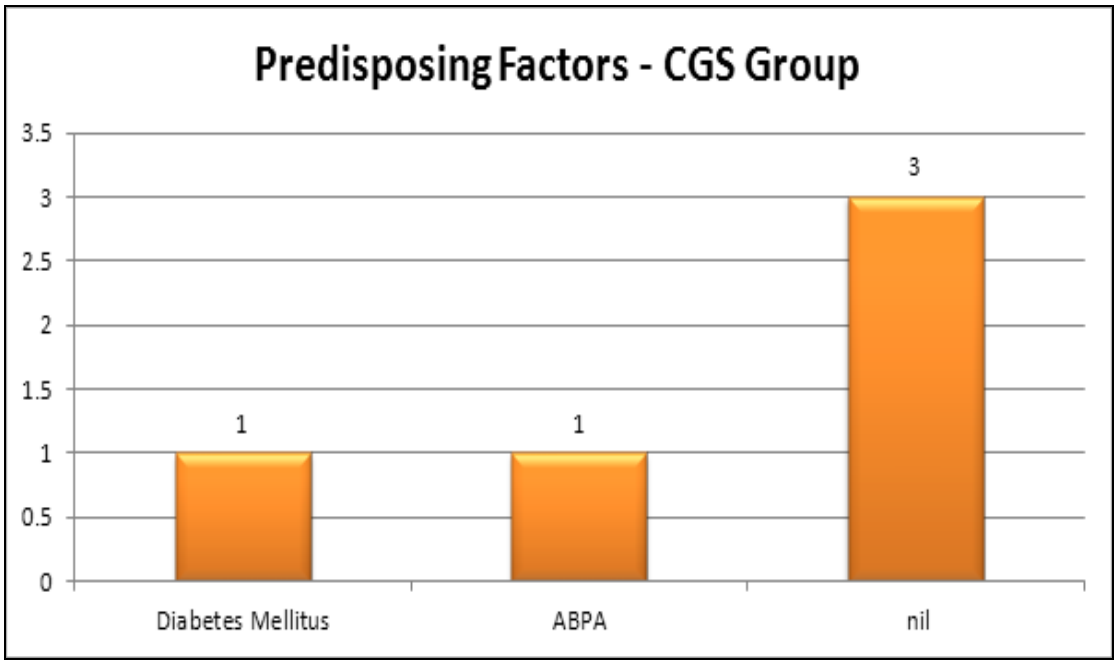
Clinical Features	AIS	CIS	CGS	AIS %	CIS %	CGS %	P value Fishers Exact Test
Fever	4	0	0	33.33	0.00	0.00	0.0274
Headache	5	1	3	41.67	7.69	60.00	0.0476
Tooth Extraction	2	1	0	16.67	7.69	0.00	0.7695
Facial Swelling	3	0	1	25.00	0.00	20.00	0.1461
Giddiness	0	0	1	0.00	0.00	20.00	0.1567
Proptosis	3	2	0	25.00	15.38	0.00	0.5665
Diplopia	1	0	0	8.33	0.00	0.00	0.5667
Loss of Vision	1	0	0	8.33	0.00	0.00	0.5667
Vision Disturbance	0	0	1	0.00	0.00	20.00	0.1567
Nasal Obstruction	0	11	1	0.00	84.62	20.00	<0.0001
Nasal Discharge	0	8	1	0.00	61.54	20.00	0.0018
Palatal Erosion	1	0	0	8.33	0.00	0.00	0.5667
Drooling of Saliva	1	0	0	8.33	0.00	0.00	0.5667

Nasal Obstruction-40%, Nasal Discharge-30%

PREDISPOSING FACTORS



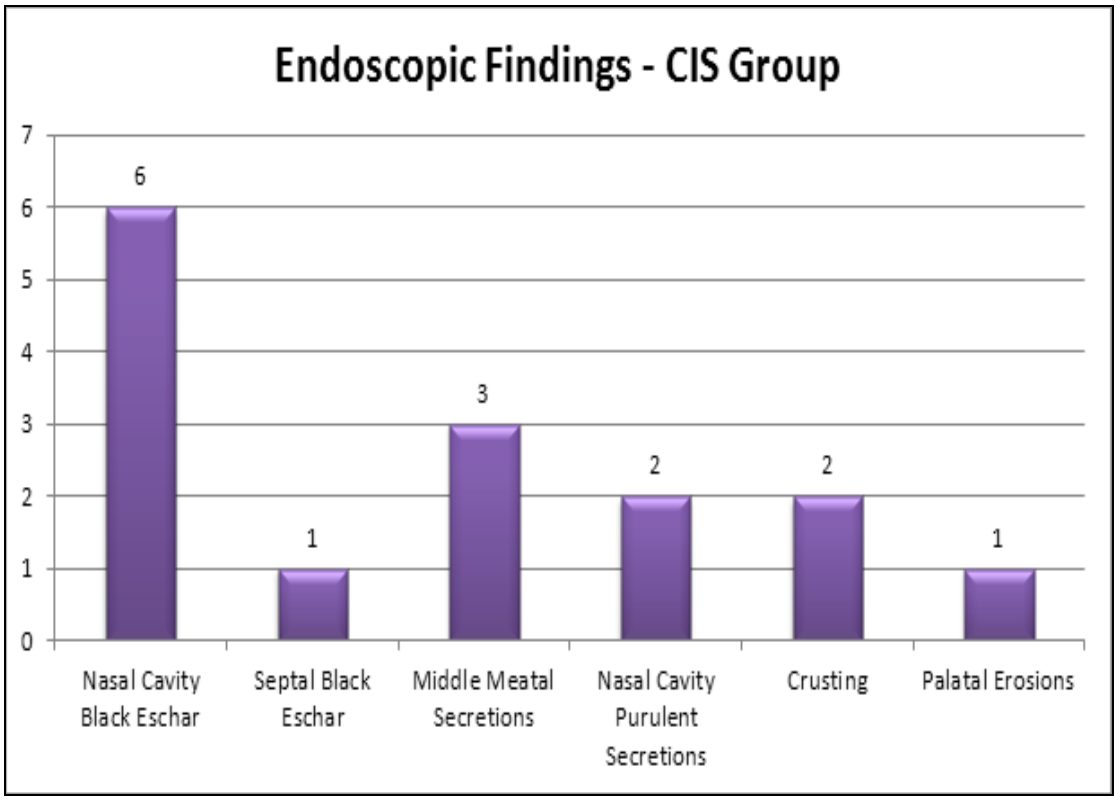

Predisposing Factors - CIS Group
14
12
10
8
6
4
2
0
12
1
1
Diabetes Mellitus
DCLD
Post renal transplantation immune suppressant

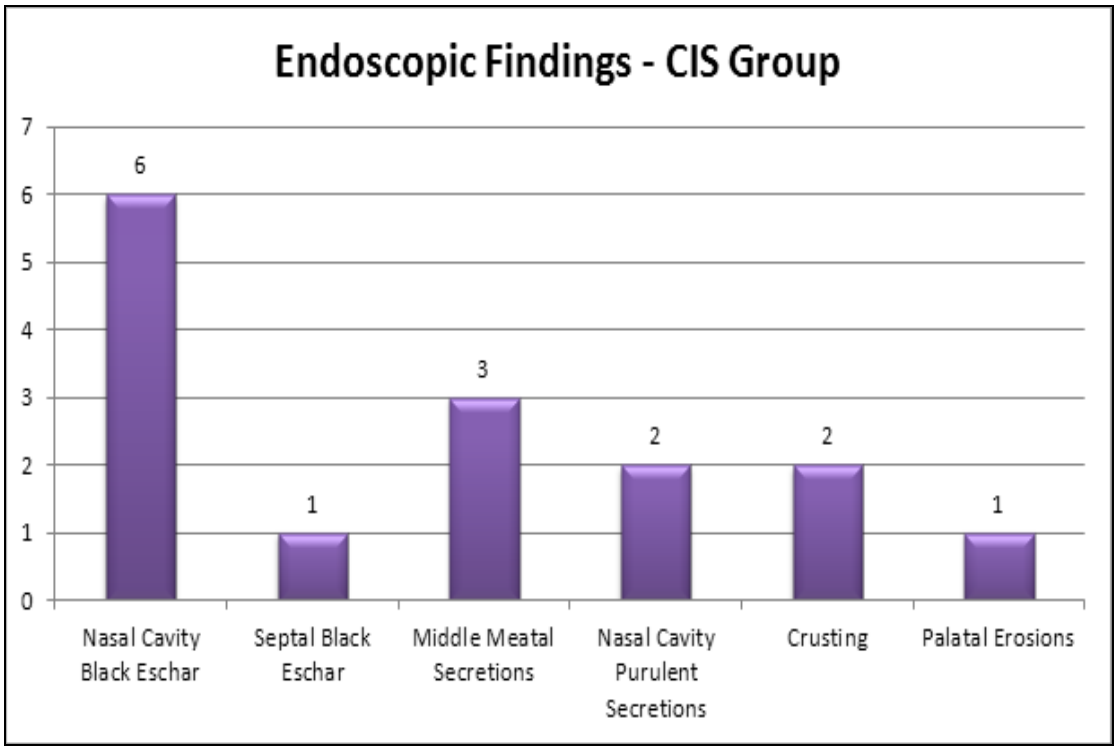

Predisposing Factors - CGS Group
3.5
3
2.5
2
1.5
1
0.5
0
1
1
3
Diabetes Mellitus
ABPA
nil

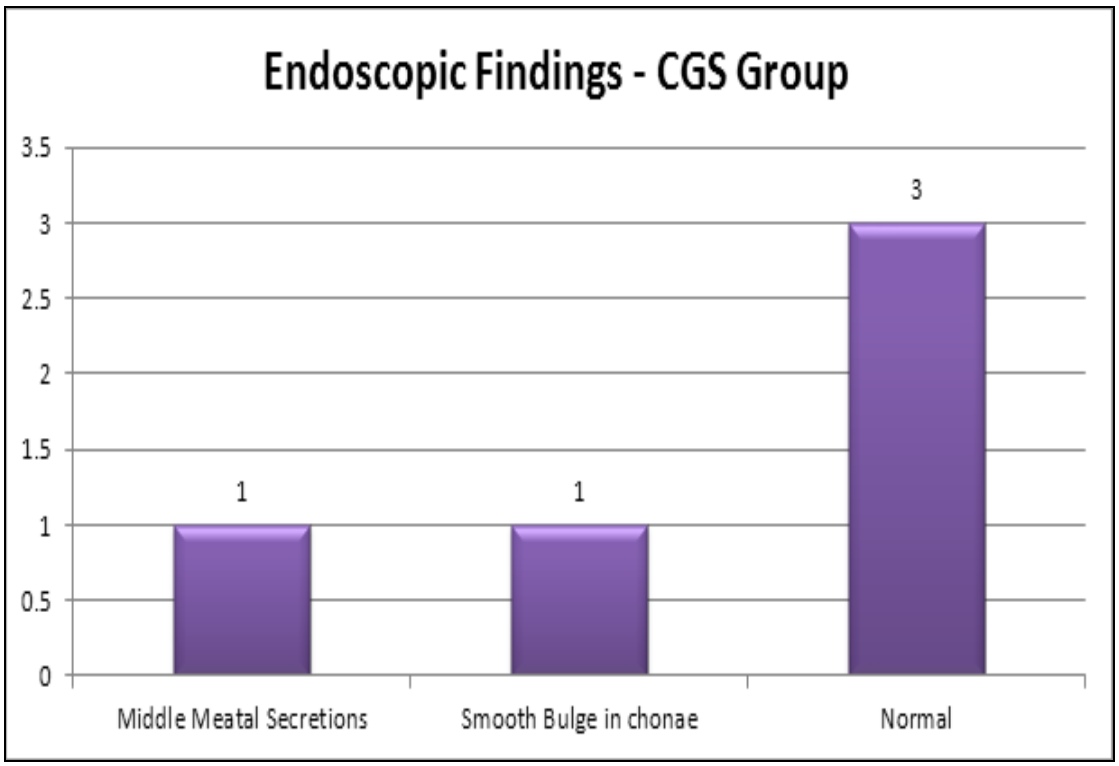
Predisposing Factors	AIS	CIS	CGS	AIS %	CIS %	CGS %	P value Fishers Exact Test
Diabetes Mellitus	13	12	1	108.33	92.31	20.00	0.0004
ABPA	0	0	1	0.00	0.00	20.00	0.1567
TB	1	0	0	8.33	0.00	0.00	0.5667
DCLD	1	1	0	8.33	7.69	0.00	>0.9999
Post renal transplantation on immune suppressant	0	1	0	0.00	7.69	0.00	>0.9999
Nil	0	0	3	0.00	0.00	60.00	0.0028

DM-87% (Among these 8% were chronic steroid users)

ENDOSCOPIC FINDINGS



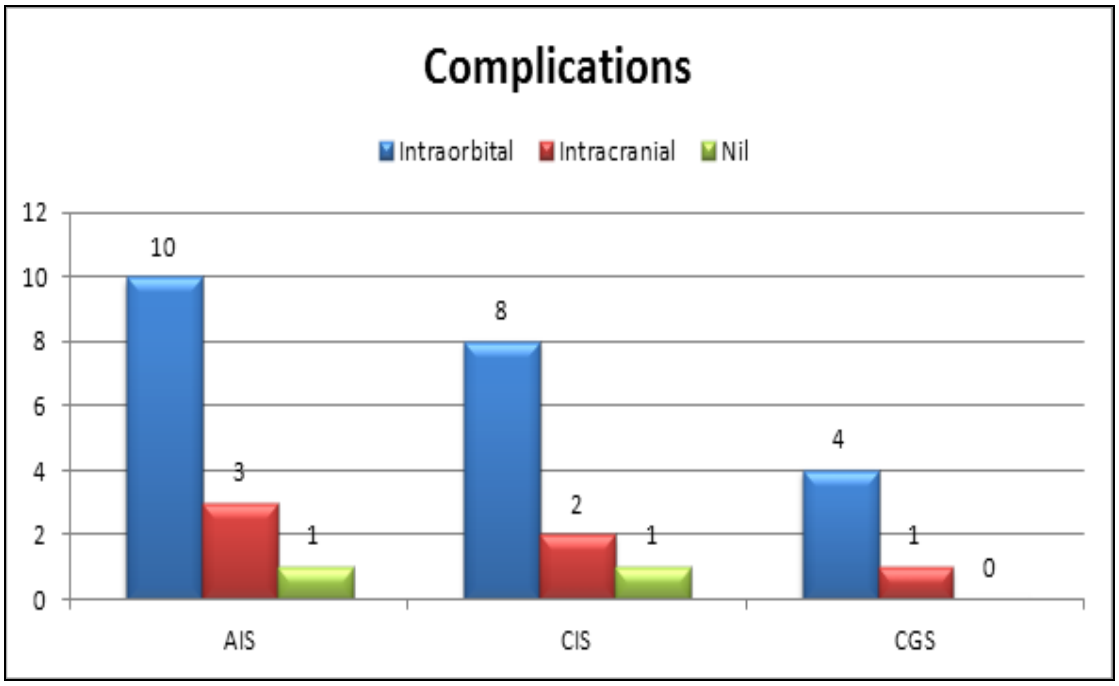




Black Escar (Nasal Cavity Palate) 40%

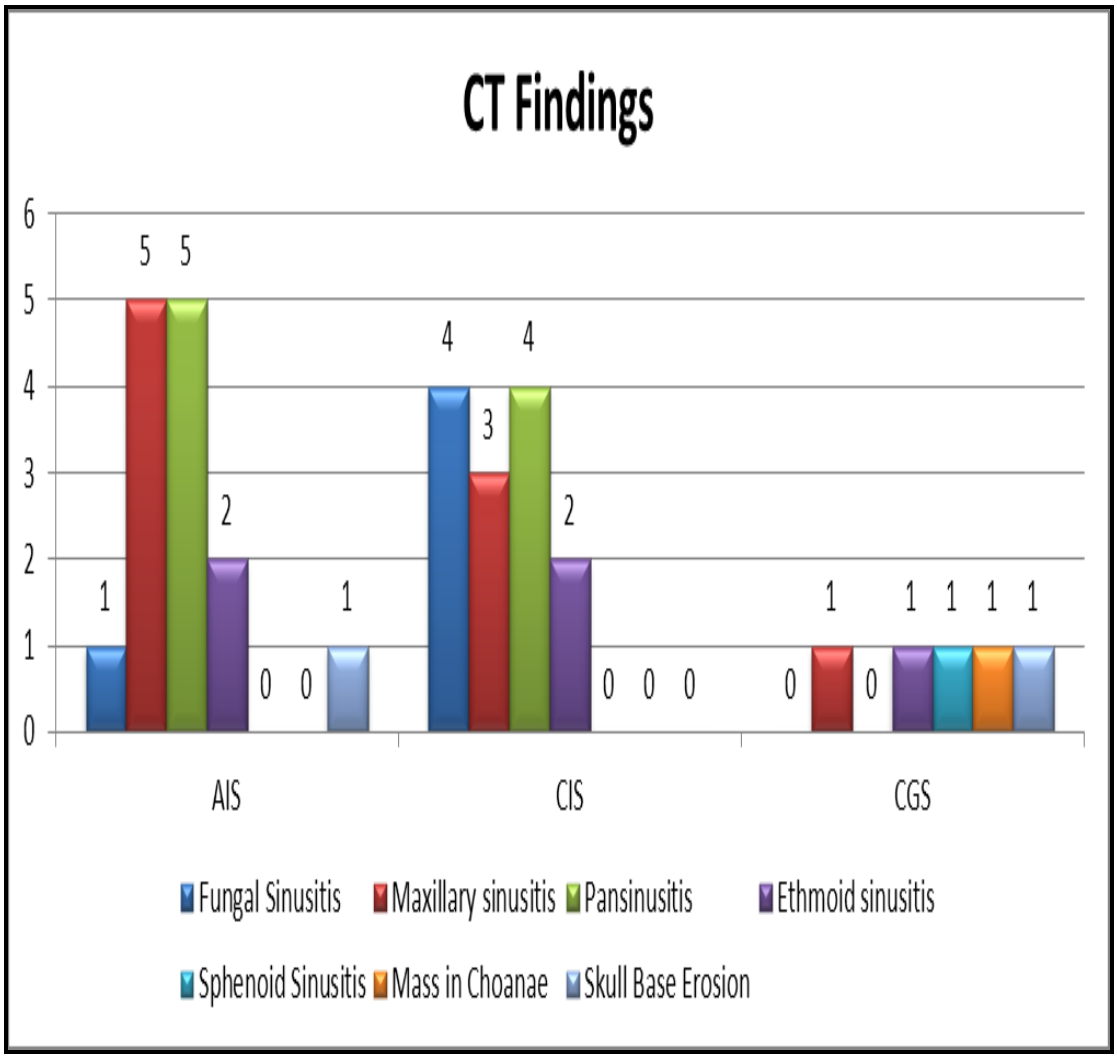
Endoscopic Findings	AIS	CIS	CGS	AIS %	CIS %	CGS %	P value Fishers Exact Test
Nasal Cavity Black Eschar	4	6	0	33.33	46.15	0.00	0.2061
Hard Palate Black Eschar	3	0	0	25.00	0.00	0.00	0.1162
Septal Black Eschar	0	1	0	0.00	7.69	0.00	>0.9999
Middle Meatal Secretions	2	3	1	16.67	23.08	20.00	>0.9999
Nasal Cavity Secretions	1	0	0	8.33	0.00	0.00	0.5667
Nasal Cavity Purulent Secretions	0	2	0	0.00	15.38	0.00	0.6414
Crusting	0	2	0	0.00	15.38	0.00	0.6414
Palatal Erosions	0	1	0	0.00	7.69	0.00	>0.9999
Sloughing	2	1	0	16.67	7.69	0.00	0.7695
Slough Covered Mass	1	0	3	8.33	0.00	60.00	0.0046
Smooth Bulge in chonae	0	0	1	0.00	0.00	20.00	0.1567
Normal	1	0	3	8.33	0.00	60.00	0.0046

COMPLICATIONS



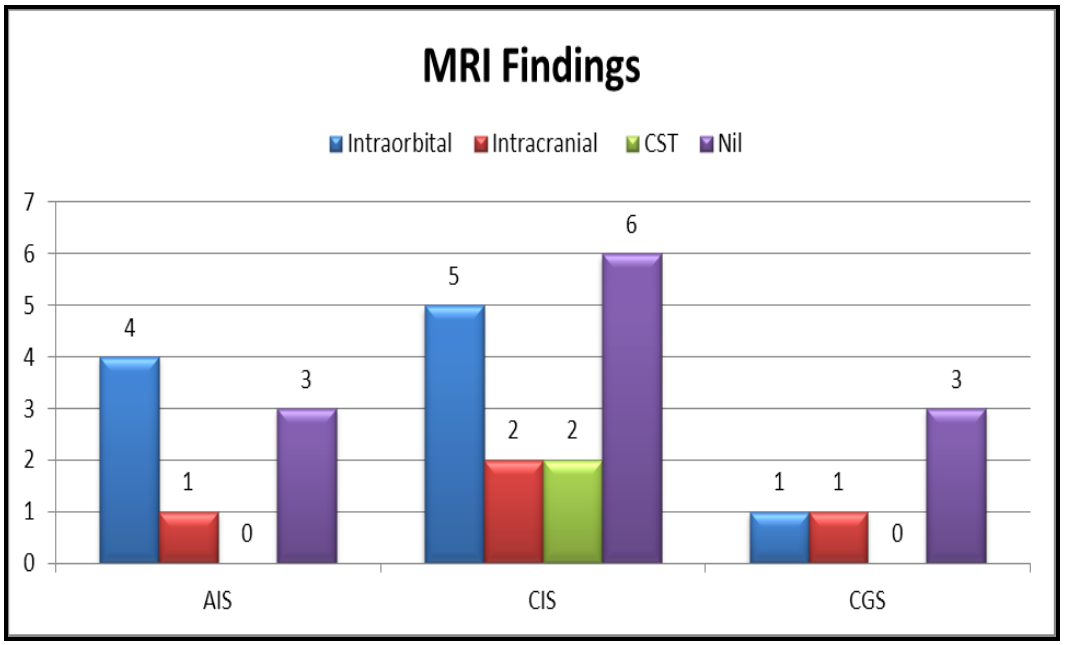
Complications	AIS	CIS	CGS	AIS %	CIS %	CGS %	P value Fishers Exact Test
Intraorbital	10	8	4	83.33	61.54	80.00	0.0496
Intracranial	3	2	1	25.00	15.38	20.00	>0.9999
Nil	1	1	0	8.33	7.69	0.00	>0.9999

CT FINDINGS


CT Findings
6
5
4
3
2
1
0
1
5
5
2
0
0
1
4
3
4
2
0
0
0
0
1
0
1
1
1
1
AIS
CIS
CGS
Fungal Sinusitis
Maxillary sinusitis
Pansinusitis
Ethmoid sinusitis
Sphenoid Sinusitis
Mass in Choanae
Skull Base Erosion

CT Findings	AIS	CIS	CGS	AIS %	CIS %	CGS %	P value Fishers Exact Test
Fungal Sinusitis (Maxillary & Ethomoid)	1	4	0	8.33	30.77	0.00	0.2199
Maxillary sinusitis	5	3	1	41.67	23.08	20.00	0.5685
Pan sinusitis	5	4	0	41.67	30.77	0.00	0.2587
Ethmoid sinusitis	2	2	1	16.67	15.38	20.00	>0.9999
Sphenoid Sinusitis	0	0	1	0.00	0.00	20.00	0.1567
Mass in Choanae	0	0	1	0.00	0.00	20.00	0.1567
Skull Base Erosion	1	0	1	8.33	0.00	20.00	0.1609

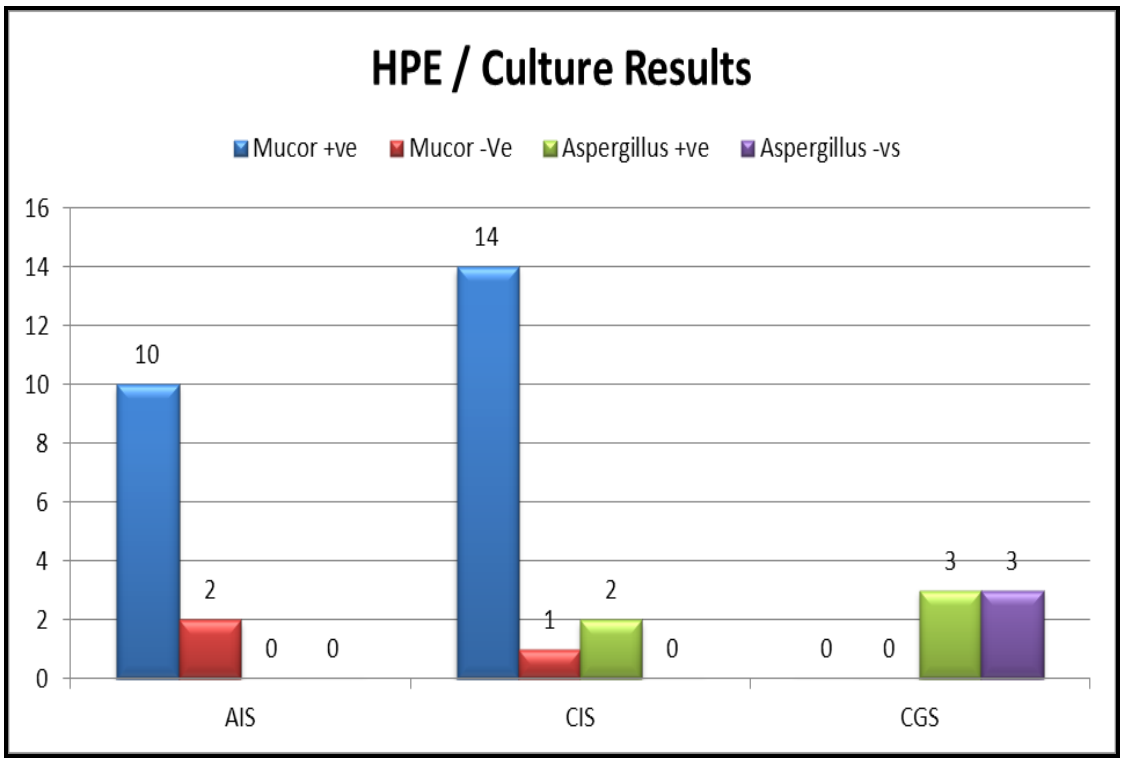
MRI FINDINGS



MRI Findings	AIS	CIS	CGS	AIS %	CIS %	CGS %	P value Fishers Exact Test
Intraorbital	4	5	1	33.33	38.46	20.00	0.8822
Intracranial	3	2	1	25.00	15.38	20.00	0.5574
CST	0	2	0	0.00	15.38	0.00	0.6653
Nil	3	6	3	25.00	46.15	60.00	0.3284

Intraorbital-33%, Intracranial-20%

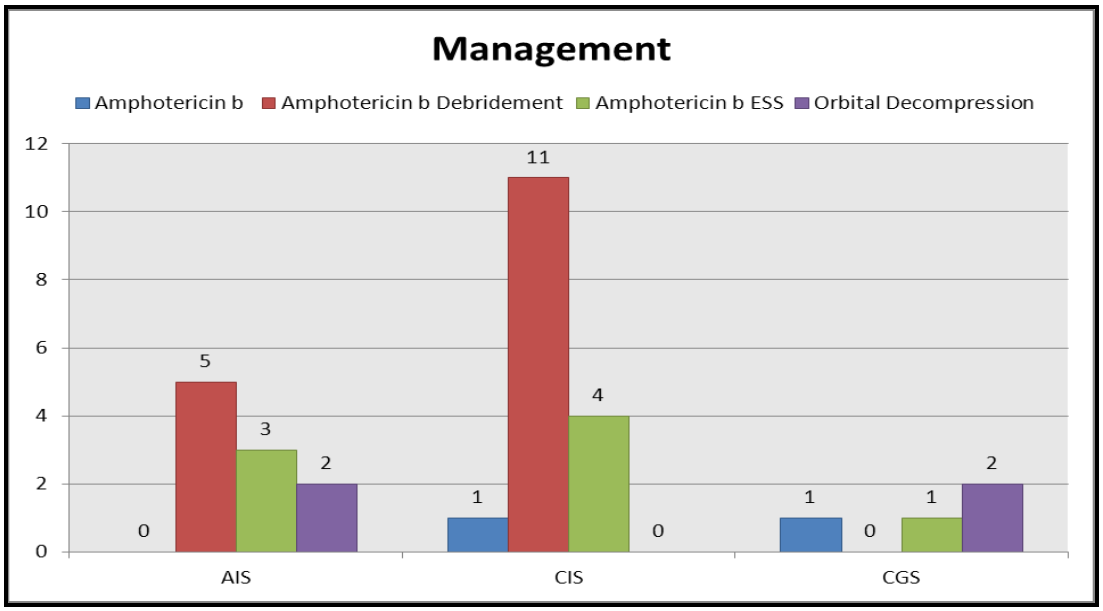
HPE / CULTURE RESULTS



HPE / Culture Results	AIS	CIS	CGS	AIS %	CIS %	CGS %	P value Fishers Exact Test
Mucor +ve	10	14	0	83.33	107.69	0.00	<0.0001
Mucor –Ve	2	1	0	16.67	7.69	0.00	>0.9999
Aspergillus +ve	0	2	3	0.00	15.38	60.00	0.0110
Aspergillus –ve	0	0	3	0.00	0.00	60.00	0.0462

Mucorales – 83%, Aspergillus- 17%

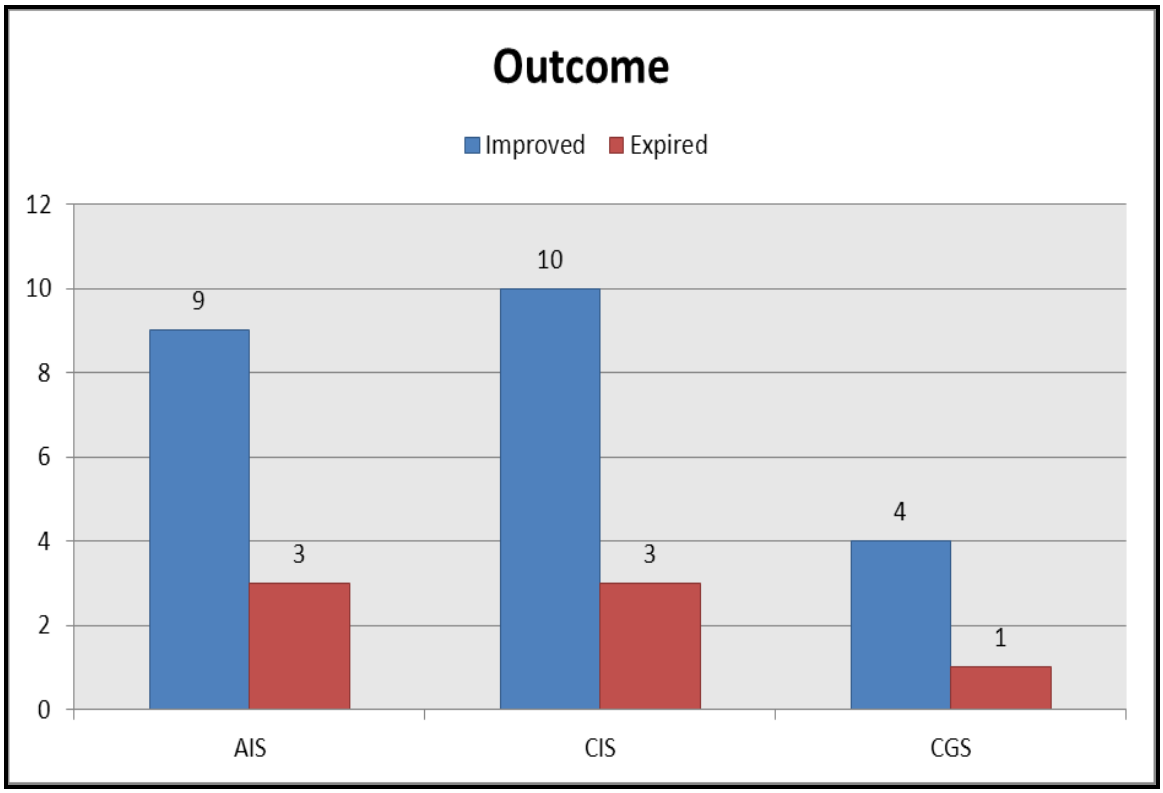
MANAGEMENT



Management	AIS	CIS	CGS	AIS %	CIS %	CGS %	P value Fishers Exact Test
Amphotericin b	0	1	1	0.00	7.69	20.00	0.3103
Amphotericin b& Debridement	5	11	0	41.67	84.62	0.00	0.0024
Amphotericin b & ESS	3	4	1	25.00	30.77	20.00	>0.9999
Orbital Decompression	2	0	1	16.67	0.00	20.00	0.0415

ESS with amputation-27%, Debridement with Amphotericin-53%

OUTCOME



Outcome	AIS	CIS	CGS	AIS %	CIS %	CGS %
Improved	9	10	4	75.00	76.92	80.00
Expired	3	3	1	25.00	23.08	20.00
Total	12	13	5	100	100	100
P value Fishers Exact Test				>0.9999		

Expired-23%

REVIEW OF LITERATURE

Bhansali Postgrad Med J 2004;80:670–674. doi: 10.1136/pgmj.2003.016030.[23]

A cohort of 23 men and 12 women with a mean (SD) age of 47.3 (14.4) years (range 18–70 years) was studied. Five patients had type 1 diabetes mellitus, 29 had type 2 diabetes mellitus, and one had secondary diabetes. Nine patients had ROCM as the first clinical manifestation of diabetes. The mean (SD) blood glucose at presentation was 20.6 (8.3) mmol/l (range 10.0 to 53.3 mmol/l) and 17 patients had ketosis/ketoacidosis. Ophthalmic symptoms and signs were pronounced: external ophthalmoplegia (89%), proptosis (83%), visual loss (80%), chemosis (74%), and eye lid gangrene (14%). Non-ophthalmic manifestations included sinusitis (100%), nasal discharge/ulceration (74%), palatal necrosis (29%), cerebral lobe involvement (20%), and hemiparesis (17%). Computed tomography/magnetic resonance imaging showed involvement of paranasal sinuses in all patients with ethmoid (86%) and maxillary (80%) sinuses being most frequently involved. Orbital involvement was observed in 80% of patients with cavernous sinus thrombosis in 11%, and internal carotid occlusion and hydrocephalus in 3% each. All were treated with amphotericin B (3–3.5 g) and 26 (74%) patients underwent appropriate surgery. Twenty one patients (68%) survived with a mean (SD) follow up of 39.6 (34.1)

months (range 10 months to 11 years). Factors related to poor survival included delay in diagnosis and treatment facial or eye lid gangrene, hemiplegia, (cerebral invasion by mucorales) treatment with amphotericin B alon.

Yohai RA, Bullock JD, Aziz AA, et al. Survival factors in rhino-orbital-cerebral mucormycosis: major review. Surv Ophthalmol 1994;39:3–22.[24]

Yohai et al reviewed 145 case reports of ROCM, 60% of them had diabetes, and analysed their ophthalmic and nonophthalmic signs and symptoms occurring at any time during the course of disease. particularly with regard to facial swelling (46% v 30%), facial parasthesias (34% v 20%), nasal ulceration or necrosis (74% v 48%), palatal necrosis (29% v 32%), and infranuclear facial palsy (46% v 22%).

Cavernous sinus thrombosis usually results from spread of infection from the orbit and appears as a filling defect within the enhancing sinus or as a lateral convexity, was evident in 11% which was comparable with others.

Ferry AP, Abedi S. Diagnosis and management of rhino-orbitocerebral mucormycosis (phycomycosis): a report of 16 personally observed cases.[25]

Ophthalmology 1983;90:1096–104. Among 13 cases, 81% of them had diabetes, visual loss. 80% reported black eschar of skin, nasal mucosa, or palate in only 19% of their patients

Otolaryngology–Head and Neck Surgery (2010) 143, 614-620[26]

"Overall survival rate of the patients in the open surgery group (4 of 7; 57.1%) was similar to that of the endoscopically treated group (9 of 19; 47.3%). Thirteen patients (50%) died of complications related to the underlying disease (9 of 13; 69.2%) and AIFRS (4 of 13; 30.7%). AIFRS-specific survival rate is 76.5 percent; 90 percent (9 of 10) and 57.1 percent (4 of 7) for endoscopic and open surgery groups, respectively. Four patients who died had pathological diagnosis of mucormycosis (*P* _ 0.52)".

Seyda Karadeniz Ugurlu*, et al (Turk J Ophthalmol 2015; 45: 169-174)[27]

"Among four patients (1 female, 3 male; age range, 55-77 years) all had diabetes mellitus and two also had chronic renal failure. All patients exhibited proptosis, sinusitis, and dark-colored lesions on the nasopharynx and/or hard palate; three patients had ipsilateral peripheral facial paralysis. Visual loss with no light perception occurred in 2 cases with severe orbital involvement and in 2 cases with limited orbital involvement. Histopathological examination of the hard palate, nasopharynx or sinus biopsy revealed typical Mucor hyphae."

Systemic liposomal amphotericin B was initiated in all patients. The patients with limited ocular involvement received amphotericin B both intravenously and by local irrigation; both patients had complete recovery. The other two patients underwent orbital exenteration; one patient died after declining systemic treatment postoperatively. Rapid diagnosis and treatment are important for the survival of rhino-orbital mucormycosis patients. With orbital involvement, surgical debridement and systemic and local treatment with antifungal agents may help avoid mutilating surgery like exenteration.

World Neurosurgery, Intracranial fungal granuloma ;Arvind dubey,MD, 2005.

22 year retrospective review of 40 patientsshows predominant symptom headache (83%), vomiting (65%). Location of PNS (40)% Frontal (25%), Anterior cranial foosa (20%), sellar/parasellar (15%). HPE Shows aspergilloma (63%) mucormycosis (18%). Microbiology analysis shows 60% Positive[28].

DISCUSSION

Among 30 cases in our study of invasive fungal sinusitis the detected species were Mucorales and Aspergillus. 25 cases of Mucormycosis and 5 cases of invasive aspergillosis were noted in our study. Both can be causative factor for acute and chronic invasive (granulomatous and non granulomatous) fungal sinusitis that have high mortality and morbidity in immunocompromised patients. Acute cases were presented with facial swelling with pain, fever followed by tooth extraction in 2 cases. In chronic cases patient mostly presented with nasal obstruction, nasal discharge, headache. Among 26 diabetic patients 87% (2 cases were chronic steroid users-8%), 6 cases (23%) were freshly diagnosed in our institution. Even at the time of presentation they can present with intra orbital, intracranial complications with poor prognosis.

Only in chronic granulomatous form association of immunosuppressive states (like diabetes mellitus) is limited in our study. Among five patients with CGFS 1 case (20%) presented with DM, 1 case (20%) presented with ABPA (Allergic broncho pulmonary Aspergillosis) other 3 cases with no predisposing factors. All CGFS cases diagnosed as Aspergillus species (100%-usually Aspergillus flavus). After sphenoidotomy and orbital decompression 1 case with POL negative improved to POL positive.

Evaluation of patients presenting with Black eschar in nasal cavity and hard palate, with resistant fever, DKA, features suggestive of fungal sinusitis with or without intraorbital or intracranial complicated patients should be made early. Black eschar in middle turbinate, septum, palate accounts 40% of cases that clinches diagnosis of Mucormycosis. The medical treatment with Amphotericin B can be empirically started before diagnostic biopsy and culture. Weekly debridement should be done to remove the necrotic debris and to reduce the fungal load for the patients.

In Kasapoglu et al study among 26 patients with 17 males and 9 females, 65% (17 cases) showed positive for mucormycosis and 35% (9cases) showed aspergillous.[26] In our study among 30 patients 20 males (67%) and 10 females (33%), 87% are diabetic. The reported species are 83% are mucor and 17% are aspergillus.

In his study 19 cases underwent endoscopic surgery and 7 cases surgical debridement was done.[26] His study also shows that 61.5% of mucormycosis and 38.5% of aspergillus cases were expired.

In retrospective study of Bhansali et al among 35 patients 75% (23cases) are males and 25% (12 cases) females. Among which 9 patients newly diagnosed as diabetic mellitus and 17 cases with diabetic ketoacidosis.[23]

CLINICAL FEATURES COMPARISON

Clinical features	Bhansali et al n=35	Yohai et al n=80	Ferry et al n=16	Our study
Nasal discharge	74	48	19	30
Facial swelling	46	30	31	13
Fever	26	36	-	13
Head ache	20	17	-	30
Tooth ache	24	7	-	10
Proptosis	83	64	13	20
Loss of vision	80	65	25	23

Comparison of clinical features of our study with others showed 74% of nasal discharge in Bhansali et al and 30% by us.

46% of facial swelling had been observed in Bhansali[23] et al and 13% by us.

Fever had been observed in 36% of cases in Yohai et al and 13% in our study.[24]

30% cases showed headache in our study and 20% by Bhansali et al.

Ophthalmological findings like proptosis and loss of vision had been reported highest of 83% and 80% in Bhansali respectively. Our study showed 20 % proptosis and 23% of loss of vision.

Tooth ache of 24% had been reperted by Bhansali et al and 10% by us.

The DNE finding in one patient in our study showed mass in the choanal region. Biopsy taken from the mass showed granulomatous lesion and when done with special stain (PAS) showed Aspergillus species to our surprise. Due to intracranial complications with cranial nerve palsy patient expired.In arvind dubey study shows predominant organism was aspergillus was revealed in HPE as 63%, mucor 18%.[28]

CT FINDINGS

CT FINDINGS	AIS	CIS	CGS	PERCENTAGE
F/S/O Fungal sinusitis (Maxillary & Ethomoid)	1	4	0	17%
Maxillary sinusitis	5	3	1	30%
Pan sinusitis	5	3	0	30%
Ethmoidal sinusitis	2	2	1	17%

In our study incidence of maxillary sinusitis 47% ethmoid sinusitis had been observed to be 33%, whereas in Bhansali et al 86% of ethmoidal sinusitis and 80% of maxillary sinusitis had been reported.[23]

COMPLICATIONS

In our study 73% cases developed intra orbital, 20% had intra cranial, 7% had cavernous sinus thrombosis as complications. Bhansal et al reported 80% of intra orbital and 11% of cavernous sinus thrombosis complications. In our study among 6 intracranial complicated cases, after debridement 2 cases (33%) improved well by debridement.

In our study for 2 cases flap cover was given for the defect in forehead and medial canthal region and graft uptake was successful.

Among 30 cases 40% ended with no morbidty and all improved well at 6 months of follow up. Among 6 intracranialy complicated patients 2 cases were directly involved without intraorbital involvement.

CULTURE:

The culture results of our study showed 88% cases to be mucormycosis out of 25 cases and 40% as aspergillus out of 5 cases whereas kasapoglu et al reported 47% of mucormycosis out of 17 cases and 89% aspergillus out of 9 cases.[26]

In spite of reduced viability of mucorales hyphae, the causative agents of mucormycosis have been isolated highest by culture in our institution due to accurate procedure followed in mycology department.

Out of 26 patients in Kasapoglu et al study 73% underwent endoscopic sinus surgery and 27% were done with surgical debridement.[26] In our study of 30 cases 27% underwent endoscopic sinus surgery and for 53% surgical debridement were done.

Among 30 cases one case of mucormycosis presented after post renal transplant and on immunosupressent therapy (mycophenolate mofetil) for past 5 years following which diabetic mellitus was detected. Patient improved well after debridement, antifungal therapy and flap cover over medial canthus region.

Among 13 cases of expired patients in Kasapoglu study 61% were affected with mucormycosis and 39% with aspergillus.[26] In our study of 30 cases 7 were expired. 86% found to have mucormycosis and 14% with aspergillus. Among 7 expired cases 2 had decompensated liver disease which was major cause of mortality than invasive fungal sinusitis.

After introduction of Amphotericin B survival rate had been improved up to 60%.[27]

It is said in Karadeniz et al study that Inspite of 4 cases with orbital involvement close monitoring, medical therapy, debridement gave good response in 2 cases.[27]

In our study many presented with orbital involvement who showed good results with close monitoring, medical therapy and debridement.Outcome of our study among 30 patients 7 cases were expired (23%).

CONCLUSION

In conclusion, Diabetes mellitus is the most common immunocompromised status to predispose to invasive fungal sinusitis.In AIFS cases are presented with intraorbital complications than chronic cases. AIFRS requires immediate medical and surgical treatment for faster recovery and also to prevent intra cranial and intra orbital complications.

Chronic cases more commonly presented with nasal obstruction,discharge.Subtypes of chronic form differentiated only by HPE.Intracranial complications can occur without orbital involvement.

The combination of anti fungal therapy, surgical debridement and improving immunosupressed state were proven to be highly efficacious in the management of invasive fungal sinusitis. In these patients who already have a poor health condition endoscopic approach is better which has less trauma.

Combination of otorhinolaryngologist, radiologist, physician, microbiologist, diabetologist, pathologist, ophthalmologist, mycologist plays a major role for successful outcome.

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PROFORMA

CASE NUMBER :

NAME :

AGE / SEX :

IP NO. :

DATE OF ADMISSION :

DATE OF DISCHARGE:

OCCUPATION :

INCOME :

ADDRESS :

COMPLAINTS OF :

NASAL OBSTRUCTION

NASAL DISCHARGE

FACIAL SWELLING

FACIAL PAIN

FEVER

TOOTH ACHE

DOUBLE VISION

VISUAL DISTURBANCES

SYMPTOMS OF INTRACRANIAL COMPLICATIONS

HEADACHE

VOMITING

SEIZURE

PAST HISTORY

HISTORY OF PREVIOUS EAR SURGERY

FAMILY HISTORY

PERSONAL HISTORY

EXAMINATION

NOSE:

EXTERNAL CONTOUR

ROOT

BRIDGE

DORSUM

SUPRATIP

TIP

ALA

COLUMELLA

PHILTRUM

ANTERIOR RHINOSCOPY

NASAL MUCOSA

INFERIOR TURBINATE

MIDDLE TURBINATE

SEPTUM

POSTERIOR RHINOSCOPY

THROAT:

ORAL CAVITY

GUMS

PALATE

CRANIAL NERVE EXAMINATION

EYE EXAMINATION

EAR

DIAGNOSIS

PLAN

INVESTIGATIONS

COMPLETE HEMOGRAM

RENAL FUNCTION TESTS

CHEST X RAY

SEROLOGICAL TESTS

ECG

DIAGNOSTIC NASAL ENDOSCOPY

BIOPSY AND CULTURE

CT PNS

MRI BRAIN

INFORMATION SHEET

We are conducting a retrospective and prospective study on **"DIAGNOSTIC APPROACH AND MANAGEMENT STRATEGIES OF INVASIVE FUNGAL SINUSITIS"**

at the Upgraded Institute of Otorhinolaryngology, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai – 600003.

- At the time of announcing the results and suggestions, name and identity of the patients will be confidential.
- Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.
- The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of Investigator **Signature of Participant**

Date :

PATIENT CONSENT FORM

Title of the Project : "DIAGNOSTIC APPROACH AND MANAGEMENT STRATEGIES OF INVASIVE FUNGAL SINUSITIS"

Institution : Upgraded Institute of Otorhinolaryngology,
Madras Medical College,
Chennai – 600003.

Name : Date :

Age : IP No. :

Sex : Project Patient No. :

The details of the study have been provided to me in writing and explained to me in my own language.

I confirm that I have understood the above study and had the opportunity to ask questions.

I understood that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without the medical care that will normally be provided by the hospital being affected.

I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).

I have been given an information sheet giving details of the study.

I fully consent to participate in the above study.

_____	_____	_____
Name of the subject	Signature	Date
_____	_____	_____
Name of the Investigator	Signature	Date

ஆராய்ச்சி தகவல்தாள்

சென்னை ராஜீவ் காந்தி அரசு பொது மருத்துவமனைக்கு வரும் மூக்குப்பகுதி மற்றும் அருகில் உள்ள பகுதிகளுக்கு பரவக்கூடிய பூஞ்சை காளான் பாதிக்கப்பட்ட நோயாளிகளை கண்டறியும் முறை மற்றும் சிகிச்சை முறைகளை அறிந்துகொள்ள மேற்கொள்ளும் ஆய்வு.

இந்த ஆராய்ச்சியில் பாதிக்கப்பட்ட நோயாளிகளை கண்டறிந்து அதற்கேற்ப அறுவை சிகிச்சை மற்றும் மருந்துகளை அளித்து அந்த சிகிச்சை முறைகளின் தன்மையைப் பற்றி ஆராய்வது.

நீங்கள் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம்.

இந்த ஆராய்ச்சியின் முடிவுகளை அல்லது கருத்துக்களை வெளியிடும் போதோ அல்லது ஆய்வின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துக்கொள்கிறேம்.

இந்த ஆய்வில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில்தான் இருக்கிறது. மேலும் நீங்கள் எந்நேரமும் இந்த ஆய்விலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியின் முடிவுகளை ஆராய்ச்சியின்போது அல்லது ஆய்வின் முடிவின் போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

ஆய்வாளரின் கையொப்பம் **பங்கேற்பாளர் கையொப்பம்**

தேதி

<u>சுய ஒப்புதல் படிவம்</u>

ஆய்வு செய்யப்படும் தலைப்பு

மூக்குப்பகுதி மற்றும் அருகில் உள்ள பகுதிகளுக்கு பரவக்கூடிய பூஞ்சை காளான் பாதிக்கப்பட்ட நோயாளிகளை கண்டறியும் முறை மற்றும் சிகிச்சை முறைகளை அறிந்துகொள்ள மேற்கொள்ளும் ஆய்வு

ஆய்வாளர் பெயர் : மரு.சி.சுஜய்குமார்

ஆராய்ச்சி நிலையம் : சென்னை மருத்துவக் கல்லூரி மற்றும்
ராஜீவ் காந்தி அரசு பொது மருத்துவமனை,
சென்னை – 3.

பங்கு பெறுவரின் பெயர் :

பங்குபெறுபவரின் எண் :

பங்குபெறுபவர் இதனை (✓) குறிக்கவும்

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது. ☐

நான் இவ்வாய்வில் தன்னிச்சையாகதான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன். ☐

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன். ☐

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும், பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான தகவல்களையும் மருத்துவர் மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக்கொள்ளவும் அதை பிரசுரிக்கவும் என் முழு மனதுடன் சம்மதிக்கின்றேன். ☐

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக்கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்து கொள்வதுடன் ‘இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்று உறுதியளிகிறேன். ☐

இந்த ஆய்வில் எனக்கு இரத்தம், திசு பரிசோதனை, சி.டி. ஸ்கேன், எம்.ஆர்.ஐ., போன்ற பரிசோதனைகள் செய்துகொள்ள சம்மதம். ☐

பங்கேற்பவரின் கையொப்பம் ..... இடம்..... தேதி.....

கட்டைவிரல் ரேகை

பங்கேற்பவரின் பெயர் மற்றும் விலாசம் .....

ஆய்வாளரின் கையொப்பம் ..... இடம்..... தேதி.....

ஆய்வாளரின் பெயர் .....

MASTER CHART

S /n	Name	Age/ sex	Clinical feature	Predisposing factors	Endoscopic findings	Diagnosis	Complications	Ct pns	Mri brain	Hpe/culture	Management	Out come
1	Chinnathambi	60/M	Nasal obstruction,Nasal discharge	DM/Bronchiolitis	Purulent secretions in rt nasal cavity	CIFS	-	Pan sinusitis	_	Mucor/ Aspergillus	Amphotericin b ESS	Improved
2	Ganesan	49/M	Nasal obstruction, proptosis lt eye	Post renal transplantation immune suppressant/DM	Black eschar in lt nasal cavity	CIFS	Intraorbital-visual loss	Lt ethmoid sinusitis	Intraorbitchronic infarct	Mucor/+	Amphotericin b Debridement ,Flap cover over lt medial canthus	Improved
3	Kumar	52/M	Rt eye proptosis ,Drooling of saliva rt side	DM/DCLD	Crust rt nasal cavity	CIFS	Intraorbital CST	F/S/O Fungal sinusitis	_	Mucor/+	Debridement	Expired
4	Babu	51/M	Headache,Giddiness	DM	Smooth bulge in choanae	CGFS	Intracranial	Mass in choanae	Intracranial	Granulomatous lesion / PAS)Aspergillus/-	Amphotericin b	Expired
5	Latha	36/F	Headache, vision disturbance	_	Normal	CGFS	Intraorbital- visual loss	Skull base erosion	Intraorbit	Aspergillus/-	Amphotericin Sphenoidotomy/Optic nerve decompression	Improved
6	Elumalai	48/M	Headache f/b tooth extraction,rt eye diplopia	DM	Slough covered mass in rt MM	AIFS	Intraorbital, Intracranial [Temporal lobe abscess]	Rt maxillary sinusitis	Rt temporal lobe abcess	Mucor/+	Amphotericin b FESS/ Orbital decompression, Craniotomy	Improved
7	Palaniyappan	48/M	Fever,Lt eye proptosis	DM/Fourniers gangrene	Lt nasal cavity black eschar	AIFS	Intraorbit	F/S/O Fungal sinusitis	Intraorbit	Mucor/+	Amphotericin b Lt Endoscopic medial maxillectomy/caldwell luc approach	Improved
8.	Ponnusamy	54/M	Fever,proptosis,Palatal erosion	DM	Slough covering both nasal cavity	AIFS	intraorbit	Pansinusitis on both sides	_	Mucor/-	Amphotericin b,Modified Denkers with total palatectomy	Improved
9	Tamilselvi	35/F	Headache, Fever,Rt facial swelling,pain	DM	Blackish eschar in MM,Oral cavity	AIFS	Intraorbit Intracranial	Pansinusitis	Infarct rt fronto temporal	Mucor/+	Amphotericin b, Debridement,Orbital enucleation/Forehead flap to cover rt cheek swelling	Improved
10	Kandhan	46/M	Pain and swelling in lt cheek,eyelid following tooth extraction	DM	Black eschar in rt MM	AIFS	Intraorbit	Rt maxillary ethmoid sinusitis	Intraorbit	Mucor/-	Amphotericin b Debridement	Improved
11	Mohanasundaram	55/M	Lt facial pain,Lt eye proptosis	DM	Black eschar in Lt nasal cavity	CIFS	Intraorbit,Intracranial CST	F/S/O Fungal sinusitis	Intraorbit Intracranial, CST	Mucor/+	Amphotericin b Debridement	Expired
12	Elumalai	47/M	Nasal obstruction, Nasal discharge	DM	MM meatal secretions rt side,Black eschar in palate	CIFS	_	Rt maxillary sinusitis	-	Mucor/+	Amphotericin b, Debridement	Improved

S /n	Name	Age/ sex	Clinical feature	Predisposing factors	Endoscopic findings	Diagnosis	Complications	Ct pns	Mri brain	Hpe/culture	Management	Out come
13	Pandiyammal	45/F	Nasal obstruction/ nasal discharge	DM	Blackish eschar in Rt MT	CIFS	_	Mucosal thickening of Rt maxillary sinus	_	Mucor/+	Amphotericin b Debridement	Improved
14	Pitchandi	55/M	Nasal obstruction/ nasal discharge	DM	crust in Lt Septum, MT	CIFS	Intra orbit- visual loss	F/S/O Lt fungal sinusitis	_	Mucor/+	Amphotericin b Debridement	Improved
15	Jagadhambal	56/F	Nasal obstruction/ nasal discharge	DM	MM secretions on both nasal cavity, palatal erosion	CIFS	Intra cranial /CST	pansinusitis	Intracranial/ CST	Mucor/+	Amphotericin b Debridement	Expired
16	Subramani	63/M	Loss of vision/ headache	DM	MM Secretions Rt nasal cavity	AIFS	Intra orbit/ Intracranial	Skull base erosion	Intraorbital,Intracranial	Mucor/+	Amphotericin b Debridement	Expired
17	Veerasamy	42/M	Headache/ facial pain	DM foot/ CAT II defaulter/ DCLD	Black Eschar in Rt nasal cavity, Palate	AIFS	Intra orbital	Pansinusitis	_	Mucor/+	Amphotericin b Debridement	Expired
18	Baskar	42/M	Nasal obstruction/ nasal discharge	ABPA	Middle meatal secretions +	CGFS	Intra orbital	Rt Ethmoid sinusitis	_	Aspergillus/+	Amphotericin b Itraconazole ESS with medial wall exploration	Improved
19	Ranagsamy	60/M	Nasal obstruction/ nasal discharge	DM	Black Eschar in lt side septum,lateral nasal wall	CIFS	Intra orbit— visual loss	Pansinusitiis	Intra orbit	Mucor/+	ESS Debridement	Improved
20	Srinivasa Ramanujam	57/M	Fever, lt eye proptosis	DM	Normal	AIFS	Intra orbital	Lt Maxillary/ Ethmoid sinusitis	Intra orbit	Mucor/+	ESS Lt Orbital decompression	Improved
21	Thenmozhi	30/F	Facial pain Rt side, Fever	DM/chronic steroid	Rt MM secretions	AIFS	_	Rt Maxillary sinusitis	_	Mucor/+	Amphotericin B ESS	Improved
22	Tamilselvi	55/F	Headache/ nasal obstruction	DM/chronic steroid	Black Eschar in rt nasal cavity,pus in MM	CIFS	Intra orbital	Pansinusitis	No acute Infarct	Mucor/+	Amphotericin B ESS,Debridement	Improved
23	Mythili	56/F	Nasal obstruction/ nasal discharge, progressive blackening of toes	DM/ Necrotising fascitis	MM secretions on both sides	CIFS	Intra orbital-visual loss	Rt pansinusitis	Intra orbit	Mucor/ rhizopus Aspergillus	Amphotericin B ESS Debridement	Improved

S /n	Name	Age/ sex	Clinical feature	Predisposing factors	Endoscopic findings	Diagnosis	Complications	Ct pns	Mri brain	Hpe/culture	Management	Out come
24	Vasudevan	45/M	Headache Vision disturbances	_	Normal	CGFS	Intra orbital- visual loss	Isolated Sphenoid sinusitis	_	Aspergillus/+	Amphotericin B Voriconazole Sphenoidotomy, orbital decompression	Improved
25	Valliyammal	55/F	Rt cheek,eyelid swelling tooth ache,fever	DM	Rt nasal cavity secretions, hard palate eschar	AIFS	Intra orbit CST	Pansinusitis	_	Mucor/+	Amphotericin B Debridement	Expired
26	Ezhilarasi	50/F	Lt facial pain Tooth ache	DM/ Lt atropic rhinitis	Rt nasal cavity purulent secretions	CIFS	Intra orbit	F/S/O fungal sinusitis	Intraorbit	Mucor/-	Amphotericin B Debridement	Improved
27	Nagoorbee	40/F	Headache Lt facial pain	DM	slough covering the palate	AIFS	Intra orbit	Pansinusitis	_	Mucor/+	Amphotericin B Debridement	Improved
28	Manavalan	43/M	Lt eyelid swelling	_	Normal	CGFS	Intra orbit	Lt maxillary sinusitis	_	Aspergillus/-	Amphotericin B ESS	Improved
29	Mathammal	68/F	Rt cheek Swelling and pain	DM	Rt side Slough covered IT	AIFS	_	Rt maxillary sinusitis	Masticator,buuccal, temporalis involvement	Mucor/+	Amphotericin b Debridement	Improved
30	Singaram	55/M	Nasal obstruction ,discharge	DM	Black eschar in Rt nasal cavity	CIFS	Intra orbit – visual loss	Rt ethmoid ,maxillary sinusitis	Intra orbit	Mucor/+	Amphotericin B, Debridement	Improved

CIFS - chronic invasive fungal sinusitis , CGFS - chronic granulomatous fungal sinusitis , AIFS - Acute invasive fungal sinusitis , DM - Diabetic mellitus, DCLD - Decompensated liver disease, MM - Middle meatus, MT - Middle Turbinate, IT - Inferior turbinate, CST - Cavernous sinus thrombosis, ESS - Endoscopic sinus surgery, Mucor-Mucormycosis, + - positive, - Negative only 3pts

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.S.Sujaykumar
Post Graduate in M.S. (E.N.T.)
Madras Medical College
Chennai 600 003

Dear Dr.S.Sujaykumar,

The Institutional Ethics Committee has considered your request and approved your study titled **"DIAGNOSTIC APPROACH AND MANAGEMENT STRATEGIES ON INVASIVE FUNGAL SINUSITIS " - NO.34032016.**

The following members of Ethics Committee were present in the meeting hold on **01.03.2016** conducted at Madras Medical College, Chennai 3

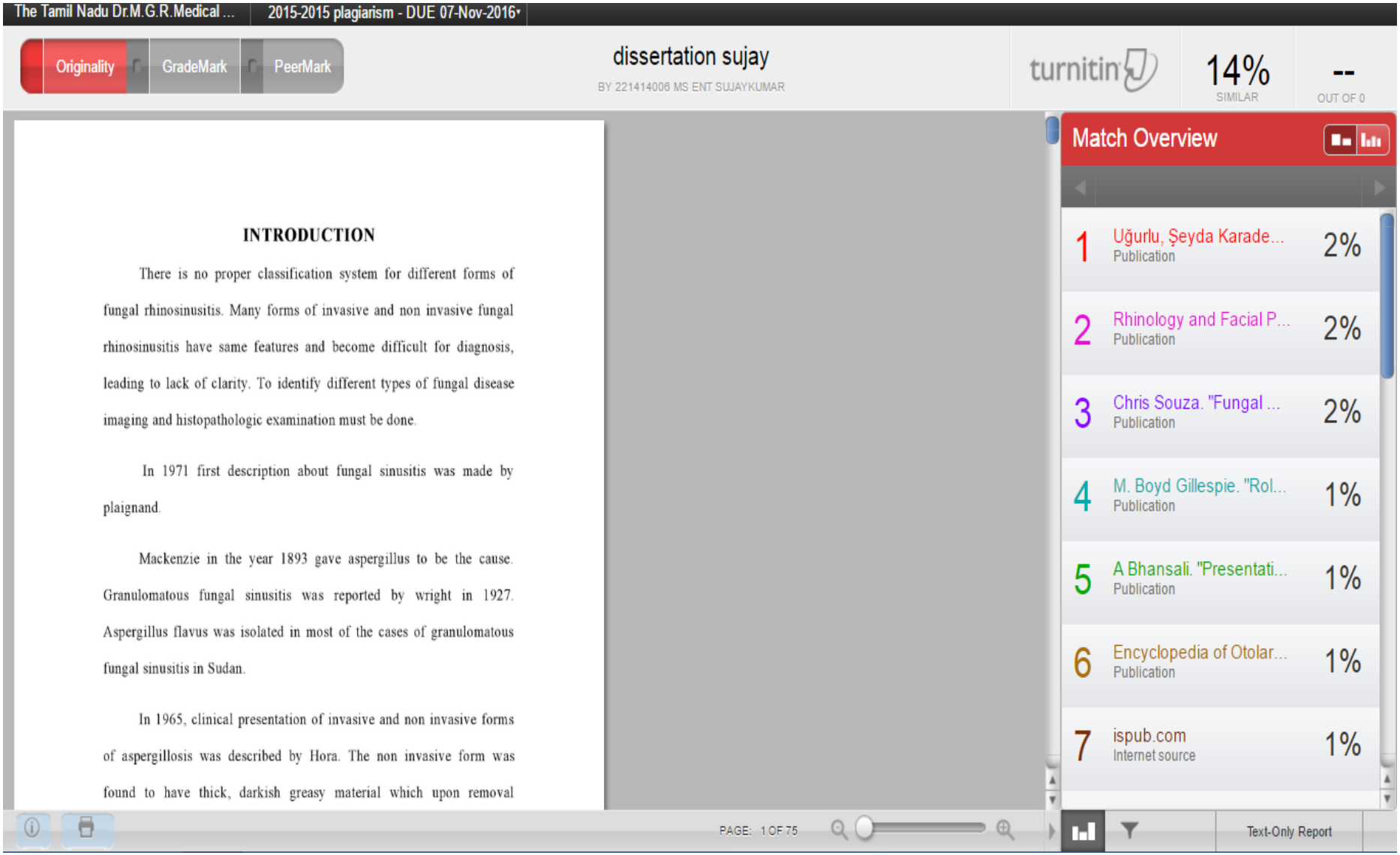
1.Dr.C.Rajendran, MD.,	:Chairperson
2.Dr.R.Vimala,MD.,Dean,MMC,Ch-3	:Deputy Chairperson
3.Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4.Prof.B.Vasanthi,MD.,Inst.of Pharmacology,MMC,Ch-3	: Member
5.Prof.P.Raghumani,MS, Dept.of Surgery,RGGGH,Ch-3	: Member
6.Dr.Baby Vasumathi, Director, Inst. of O&G,Ch-8	: Member
7.Prof.M.Saraswathi,MD.,Director, Inst.of Path,MMC,Ch-3	: Member
8.Prof.Srinivasagalu,Director,Inst.of Int.Med.,MMC,Ch-3	: Member
9.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person
10.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
11.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary - Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE.
MADRAS MEDICAL COLLEGE
CHENNAI-600 003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INTRODUCTION
There is no proper classification system for different forms of fungal rhinosinusitis. Many forms of invasive and non invasive fungal rhinosinusitis have same features and become difficult for diagnosis, leading to lack of clarity. To identify different types of fungal disease imaging and histopathologic examination must be done.
In 1971 first description about fungal sinusitis was made by plaignand.
Mackenzie in the year 1893 gave aspergillus to be the cause. Granulomatous fungal sinusitis was reported by wright in 1927. Aspergillus flavus was isolated in most of the cases of granulomatous fungal sinusitis in Sudan.
In 1965, clinical presentation of invasive and non invasive forms of aspergillosis was described by Hora. The non invasive form was found to have thick, darkish greasy material which upon removal
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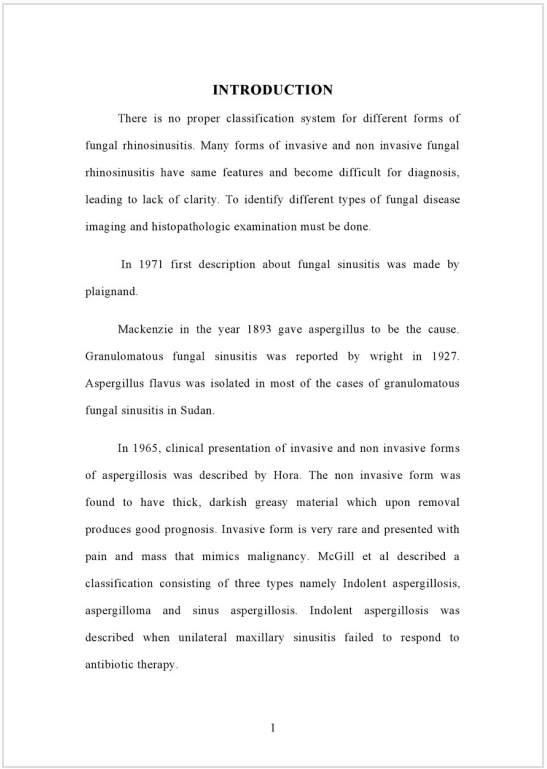

INTRODUCTION

There is no proper classification system for different forms of fungal rhinosinusitis. Many forms of invasive and non invasive fungal rhinosinusitis have same features and become difficult for diagnosis, leading to lack of clarity. To identify different types of fungal disease imaging and histopathologic examination must be done.

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In 1965, clinical presentation of invasive and non invasive forms of aspergillosis was described by Hora. The non invasive form was found to have thick, darkish greasy material which upon removal produces good prognosis. Invasive form is very rare and presented with pain and mass that mimics malignancy. McGill et al described a classification consisting of three types namely Indolent aspergillosis, aspergilloma and sinus aspergillosis. Indolent aspergillosis was described when unilateral maxillary sinusitis failed to respond to antibiotic therapy.

1